Fred Hutch Cancer Center

16th Annual Hematology Oncology Review Course

October 6-10, 2025

Question & Answer

UW Medicine

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Monday, October 6

Anal Cancer : Andrew Coveler, MD

Question 1: A 48-year old woman presents with rectal bleeding and pain. On examination she is found to have a 3 cm squamous cell carcinoma of the anal canal. Staging work up reveals no evidence of regional lymph node enlargement or distant metastases. Which of the following is the most appropriate treatment?

A) Endoscopic ultrasound and transanal excision
B) Abdominoperineal resection
C) Chemoradiotherapy using 5-FU or Capecitabine and Mitomycin C
D) Induction chemotherapy with 5-FU and cisplatin followed by definitive chemoradiotherapy with 5-FU or capecitabine.

ANSWER: C

Rationale: Localized squamous cell carcinoma of the anal canal is managed with definitive, 5-FU/mitomycin-based chemoradiotherapy. Surgery is typically used as a salvage treatment for patients with recurrent disease following radiation. Local excision is reserved for small tumors that are well-differentiated or incidentally removed at the time of hemorrhoidectomy. Finally, induction therapy with cisplatin/5-FU followed by chemoradiotherapy with cisplatin/5-FU has been compared to chemoradiotherapy with 5-FU/mitomycin-C. The 5-FU/mitomycin-C arm was found to be superior with regard to overall survival, and remains the standard of care. Capecitabine appears to be as good if not better than 5-FU though it may have increased local toxicities.

Question 2: A 67-year old man presents with rectal bleeding and is found to have a 2cm squamous cell carcinoma of the anal canal. Staging workup reveals inguinal lymphadenopathy, retroperitoneal lymphadenopathy and innumerable lung lesions consistent with metastatic disease. Which of the following is the most appropriate treatment?

A) 5FU - Cisplatin
B) Carboplatin + Paclitaxel
C) Carboplatin + Paclitaxel + Retifanlimab
D) Pembrolizumab

Answer: C

Rationale: Metastatic squamous cell carcinoma of the anal canal is managed with systemic treatment if definitive treatment is not obtainable. 5FU Cisplatin had been the standard treatment since 1999. Rao et al published in 2020 the InterAACT trial which demonstrated that Carboplatin + Paclitaxel was better tolerated and increased overall survival. Rao et al published in 2025 that the addition of retifanlimab improved PFS (and OS) with the addition of the anti PD1 agent retifanlimab.

Colorectal Cancer : Stacey A. Cohen, MD

Question 1: For patients with resected stage III colon cancer, which of the following is NOT correct:

A) 3 months of adjuvant chemotherapy is sufficient for low-risk patients.
B) Chemotherapy-induced peripheral neuropathy leads to permanent neuropathy in a subset of patients.
C) Chemotherapy should be initiated 4-8 weeks from surgery
D) Adjuvant cetuximab is beneficial for KRAS/NRAS-wildtype disease

Answer: D

Rationale: Six months of an oxaliplatin doublet chemotherapy (either with 5-FU [FOLFOX regimen] or capecitabine [CAPOX regimen]) was the standard of care for many years. The IDEA study randomized >12,000 patients to 3 vs. 6 months of FOLFOX/CAPOX. 3 months of chemotherapy nearly met the predefined statistical threshold for non-inferiority in low-risk (T1-3 N1) patients and is now accepted to be sufficient for these patients (A). The IDEA study was designed to mitigate undue toxicity from unnecessary chemotherapy for patients, namely oxaliplatin-induced peripheral neuropathy. Both the IDEA and MOSAIC studies have noted that a substantial percent of patients will experience neuropathy during chemotherapy and this can be permanent (B). Meta-analyses suggest that the ideal time to initiate adjuvant chemotherapy is 4-8 weeks after surgery (C). There has been no proven benefit to biologic agents in the adjuvant setting, including cetuximab (as was studied in N0147 and PETACC-8), even when accounting for molecular features (D).

Question 2: A 56yo man presents with a low rectal mass. MR pelvis shows a T4N1 cancer that is below the peritoneal reflection and 2cm from the anal verge. The preferred treatment plan is:

A) Long-course chemoradiation, surgery, adjuvant chemotherapy
B) Short-course radiation, surgery, adjuvant chemotherapy
C) Long-course chemoradiation, neoadjuvant chemotherapy, surgery
D) Surgery, adjuvant chemotherapy, adjuvant chemoradiation

Answer: C

Rationale: Neoadjuvant chemoradiation is standard of care for stage II-III rectal cancer to decrease pelvic recurrence and minimize the morbidity associated with adjuvant radiation therapy (D). The standard paradigm for the treatment of rectal cancer has been neoadjuvant chemoradiation, followed by surgery, and then adjuvant chemotherapy (A). A newer option is to use short-course radiation therapy (B) instead of long-course chemoradiation. However, the paradigm is shifting towards total neoadjuvant therapy (TNT), i.e. (chemo)radiation and chemotherapy given in the neoadjuvant setting, with surgery reserved for the final phase of treatment (C). For higher risk patients, TNT is beneficial as it exposes patients to systemic chemotherapy earlier in the treatment course. It also is associated with a higher frequency of complete clinical response. This is the preferred approach in this case as this patient has T4 disease and a distal tumor.

Question 3: 52yo man is diagnosed with colorectal cancer with sigmoid primary and 10 liver metastases. Molecular testing reveals intact mismatch repair and a BRAF V600E mutation. What is the best first-line therapy?

A) FOLFIRINOX + bevacizumab

B) FOLFOX + cetuximab

C) FOLFOX + encorafenib + cetuximab

D) Nivolumab + ipilimumab

Answer: C

Rationale: Biomarkers are helpful in selecting which targeted therapy agents may be beneficial or harmful for a particular patient. The BREAKWATER trial established encorafenib and cetuximab with FOLFOX as the standard for metastatic colorectal cancers with BRAF V600 mutations that are MSS (C). The BRAF mutations predicts lack of benefit from anti-EGFR therapy, such as cetuximab or panitumumab, without the BRAF blockade (B). While FOLFIRINOX + bevacizumab is a good first-line choice, it is not biomarker selected and patients with BRAF-mutant disease do not do as well without the BRAF inhibition (A). Immunotherapy is highly effective for microsatellite unstable / mismatch repair deficient tumors, but is not effective for MSS/intact MMR cancers (D).

Question 4: Which of the following chemotherapy regimens is useful for metastatic colorectal cancer

A) Trifluridine-tipiracil/nivolumab for a patient refractory to 5-FU, oxaliplatin, irinotecan, and cetuximab
B) Oxaliplatin/cetuximab for a RAS/RAF wildtype patient unable to tolerate 5-FU
C) FOLFIRI + bevacizumab after progression on FOLFOX + bevacizumab
D) Maintenance oxaliplatin after 4 months of FOLFOX with a partial response

Answer: C

Rationale: There are 5 chemotherapy agents that form the basis for metastatic colorectal cancer treatment: 5-FU, oxaliplatin, irinotecan, bevacizumab, cetuximab. These can be given in combination, and some as single agent. There has been no proven benefit for oxaliplatin given without 5-FU and so oxaliplatin/cetuximab would not be a recommended option (B). Patients who do well on therapy can be considered for de-escalation to maintenance therapy as long as they have at least stable disease. There are many options for maintenance regimens, but all consistent of a fluoropyrimidine, a biologic agent (anti-VEGF or anti-EGFR), or both. Oxaliplatin maintenance has not been studied and would not be recommended as this would not help to mitigate the associated toxicity (B). After progression on first-line therapy, either the chemotherapy backbone or the biologic agent should be changed when selecting second-line therapy. Trials of continuation of the biologic (such as FOLFOX + bevacizumab → FOLFIRI + bevacizumab) have demonstrated benefit to continuing the biologic at progression and this is a viable treatment strategy (C). For refractory colorectal cancer, trifluridine-tipiracil has demonstrated benefit compared to placebo. This may be enhanced by combining it with bevacizumab. There is no data for combining it with nivolumab, though this has been studied with regorafenib (A).

Testicular Cancer : Todd Yezefski, MD, MS

Question 1: 25yo male has a self-detected R testicular mass. Orchiectomy shows a 3cm seminoma, and CT CAP demonstrates enlarged aortocaval lymph nodes measuring up to 1.8cm. Tumor markers 4 weeks after orchiectomy are notable for AFP 120, HCG 53, and LDH 178. Which of the following is the recommended treatment?

A) RPLND
B) Radiation therapy
C) Chemotherapy with BEP x3
D) Repeat tumor markers in 2 weeks and then make a decision

Answer: C

Rationale: While pathology only showed seminoma, his AFP is significantly elevated. This is higher than can be attributed to non-malignant causes, and therefore he should be treated as a nonseminoma. With elevated tumor markers and enlarged lymph nodes, he should treated with chemotherapy with BEP for 3 cycles.

Question 2: 31yo male with stage IIB nonseminomatous germ cell tumor (pT2N2M0S1) has treatment with BEP x3. Post-chemotherapy CT CAP shows a residual retroperitoneal mass measuring 2cm. Tumor markers have normalized. What should be done next?

A) Surveillance
B) Radiation to the residual mass
C) PET-CT performed 6-12 weeks after completing chemotherapy
D) RPLND

Answer: D

Rationale: Post-chemotherapy management of non-seminoma includes resection of residual masses if they are >1cm. ~50% of the time there is fibrosis alone,;10% of the time there is viable carcinoma—in which case he would need additional chemotherapy; and 40% of the time there is teratoma. As teratoma is not chemo- or radio-sensitive, it must be removed surgically.

Pancreatic Cancer : Rachael Safyan, MD
Question 1:

- 66 year-old woman, ECOG performance status 0-1
- No family history of malignancy. Ashkenazi Jewish descent.
- Locally advanced mass in the head of the pancreas with bilobar liver metastases. Biopsy of a liver lesion confirmed moderately differentiated adenocarcinoma.
- CA 19-9 = 52,174
- Germline testing: loss-of-function BRCA2 mutation.
- Received mFOLFIRINOX x 6 months with good minimal side effects.
- RECIST response. CA 19-9 = 32 U/mL.

True or False?

Early germline genetic testing for all patients with pancreatic cancer with a multigene panel is standard practice.

Answer: True

Rationale:

- Depending on geographic region, 10-20% of pancreatic cancer cases are hereditary, with mutations in BRCA1 and BRCA2 being the most common.
- Clinical risk factors such as family history of cancer and young age of onset are not reliable predictors for which patients may carry one of these predisposing mutations.
- 2018: NCCN recommended that all pancreatic cancer patients should receive germline testing, regardless of family history.

Next plan of care?

A) Continue FOLFIRINOX until progression/toxicity
B) 5-FU-based maintenance therapy
C) Biomarker-directed maintenance therapy with Olaparib
D) Treatment break/observation

Answer: C

Rationale:

- For patients with a germline BRCA1/2 mutation, after at least 16 weeks of initial platinum-based chemotherapy, for those without disease progression, discontinue chemotherapy and initiate maintenance therapy using the PARP inhibitor Olaparib (POLO trial).
- The optimal timing of Olaparib in this setting is not established.
- PARP activity is essential for the repair of single-strand DNA breaks via the base excision repair pathway. In the setting of gBRCA1/2, cancer cells have defective homologous recombination repair function, and the unrepaired DNA breaks that result after treatment with PARP inhibitors eventually lead to cancer cell death ("synthetic lethality").
- Maintenance olparib compared with placebo was associated with significant improvement in mPFS, the primary endpoint (7.4 vs 3.8 mo, HR 0.53) and twice as many patients were progression free at 2 years (22 vs 9.6%). Overall survival was similar in both arms.

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Which of the following choices is the best next step?

A) Upfront surgical resection
B) Chemoradiation followed by surgery then adjuvant mFOLFIRINOX
C) Neoadjuvant mFOLFIRINOX then re-evaluate by a multi-disciplinary team
D) Chemoradiation alone

Answer: C

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What treatment plan would you recommend?

A) Gemcitabine + nab-paclitaxel
B) 5FU + nanoliposomal irinotecan
C) Gemcitabine + erlotinib
D) Dabrafenib + trametinib
E) Gemcitabine + cisplatin

Answer: D

Rationale:

- BRAF alterations are observed in approximately 2% of pancreatic cancer patients.
- NCI-MATCH basket trial
  - 35 solid tumors (3 pancreatic cancer) harboring BRAF V600 mutation
  - Treatment: dabrafenib + trametinib
  - 1 pancreatic cancer patient had stable disease as best response.
  - ORR was 35% for all patients
  - PFS and OS rates were 11.4 and 28.6 months, respectively
  - Led to FDA approval of this combination in pretreated cancers with *BRAF V600E* mutations

Cholangiocarcinoma : Gentry King, MD

Question 1: A 46 yr old female's recent CT scan has shown progressive disease on gemcitabine cisplatin and durvalumab. She was found to have an FGFR2-SORBS1 fusion on tumor molecular profiling.

What adjunctive medicine should she be taking while on pemigatinib FGFR2 targeted therapy?

A) Hydroxyurea
B) Calcium + Vitamin D
C) Magnesium phosphate
D) Sevelamer

Answer: D

Rationale: Patients on FGFR2 inhibitors will experience hyperphosphatemia as an on-target treatment toxicity and taking a phosphate binder on days of pemigatinib treatment is recommended to mitigate hyperphosphatemia

Question 2: A fit 55 yr old male was incidentally found to have a 3cm mass in the liver after getting a CT scan for flank pain to rule out kidney stones. He was taken to surgery and hepatectomy revealed findings consistent with a 3cm intrahepatic cholangiocarcinoma with lymphovascular invasion, negative margins and lymph nodes, no distant metastatic disease. Pathologic stage pT2N0Mx. Molecular testing shows an IDH1 R132C alteration. You discuss adjuvant treatment and recommend:

A) Observation
B) Capecitabine adjuvant therapy
C) Gemcitabine and cisplatin adjuvant therapy
D) Ivosidenib Adjuvant therapy

Answer: B

Rationale: Patient is at risk for recurrence, has intrahepatic CCA, fit for adjuvant treatment. No clear data at this time to show Gem Cis better than Cape. Ivosidenib is not used for adjuvant therapy, only for previously treated advanced BTC

Esophageal/Gastric Cancer : Veena Shankaran, MD

Question 1: A 52 y.o. healthy male is diagnosed with stage III (uT3N1) GE junction adenocarcinoma. He undergoes chemoradiation therapy with weekly carboplatin and paclitaxel and then goes on to receive esophagectomy. Final pathology from the resection reveals a near complete pathologic response, with negative nodal involvement (ypT1N0).

What should the next steps in management be?

A) Additional chemotherapy with FLOT-4 x 4 cycles in the postoperative setting?
B) Surveillance per NCCN guidelines
C) Adjuvant nivolumab therapy x 6 months
D) Adjuvant nivolumab x 1 year
E) Adjuvant pembrolizumab x 1 year

Answer: D

Rationale: Based on results from the Checkmate 577 trial, adjuvant nivolumab improves DFS in patients with non complete pathologic response after trimodality therapy. If this patient is healthy without contraindications to nivolumab, it should be offered.

Question 2: A 62 yo healthy woman with Her2 positive adenocarcinoma receives first-line therapy with FOLFOX + trastuzumab + pembrolizumab. After about 6 months of therapy, scans show disease progression (new and enlarging liver lesions) and rising tumor markers.

What would be viable second line therapies to consider?

A) Fam-trastuzumab-deruxtecan
B) FOLFIRI + trastuzumab
C) Irinotecan
D) Paclitaxel + ramucirumab
E) TAS-102
F) A, C, and D

Answer: F

Rationale: There are no data to support continuing trastuzumab into second line therapy after disease progression. TAS-102 is only approved in the 3rd line setting. Answers a., c., and d. are all supported by evidence in second line setting.

Gastrointestinal Neuroendocrine Tumors : David B Zhen, MD

Question 1: 56-year-old woman presents with many months of vague right sided abdominal pain and loose stools. A CT abdomen/pelvis identified a mass in the ileum along with multiple liver and retroperitoneal metastases. Biopsy of the liver identified a well differentiated, grade 1 (Ki-67 <3%) neuroendocrine tumor (NET). 68Gallium-dotatate PET scan identifies strong somatostatin receptor expression in all lesions seen on the CT abdomen/pelvis. Which of the following are reasonable treatment options?

A) Somatostatin analogs
B) Everolimus
C) Peptide receptor radionuclide therapy with 177Lu-dotatate
D) Sunitinib
E) A, B, C
F) All of the above

Answer: E

Rationale: This patient has a metastatic well differentiated, grade 1 NET originating from the small intestine with ileal mass seen on imaging. All of the above options are reasonable treatment options except for sunitinib which was only studied in and approved for advanced NET of pancreatic origin (pNET).

Question 2: 42 year old male is diagnosed with metastatic pancreatic neuroendocrine tumor with extensive metastases to the liver and bone. He is quite symptomatic from his disease with abdominal and bone pain. Pathology from a liver biopsy identified well differentiated neuroendocrine tumor with Ki-67 index of 25%. Ga68 dotatate-PET scan is done and shows lack of somatostatin receptor expression in any of his tumors. His liver enzymes as well as other laboratory parameters are normal, and his ECOG performance status is 1. Which of the following therapies would be most appropriate?

A) Somatostatin analogs
B) Capecitabine + Temozolomide (CAPTEM)
C) Peptide receptor radionuclide therapy with 177Lu-dotatate
D) Carboplatin + Etoposide
E) Nivolumab + Ipilimumab

Answer: B

Rationale: This patient has a metastatic well differentiated, grade 3 NET based on 2019 WHO Classification. This is different from a poorly differentiated neuroendocrine carcinoma (NEC) based on a well differentiated status and also a Ki-67 index on the lower end (i.e. 20-55%). Given this information, treatments for NEC (such as carboplatin + etoposide) and nivolumab + ipilimumab are anticipated to be less beneficial and associated with increased toxicity. Therapies for NET would usually be preferred. Given this and the pancreatic origin (which are most response to cytotoxic chemotherapy), CAPTEM would be preferred based on the results of ECOG-ACRIN EA2211. Somatostatin analogs and PRRT would not be appropriate in setting of a NET that does not express somatostatin receptors based on the negative dotatate-PET scan.

Renal Cell Carcinoma : Scott S. Tykodi, MD, PhD

Question 1: A recognized hereditary genetic syndrome is associated with an increased risk for developing renal cell carcinoma with each of the following histologic subtypes EXCEPT:

A) Clear cell
B) Papillary
C) Chromophobe
D) TFE3-translocation associated RCC

Answer: D

Aim: Recognize that RCC tumors with the most common histologies including clear cell, papillary and chromophobe, can be associated with hereditary genetic syndromes.

Rationale: Medical Oncologists serve an important role in identifying at-risk patients for proper Genetics consultation and screening. Early identification of affected family members for longitudinal surveillance should facilitate the detection and treatment of small renal tumors before progression to metastatic disease. The importance of screening for hereditary RCC has been emphasized by the recent addition of a "Hereditary Renal Cell Carcinomas" section in NCCN guidelines.

Early age at diagnosis of RCC is an important risk factor for identifying hereditary RCC. Although translocation RCC appears in a much younger patient age range than for other RCC subtypes, the common genetic lesion (TFE3-translocation) associated with this diagnosis is a somatic event within the tumor, and is not a germ line abnormality.

References:

- NCCN Kidney Cancer Guidelines v1.2026
- Argani, P. MiT family translocation renal cell carcinoma. Semin Diagn Pathol (2015) 32:103-13.

Question 2: True or False: Pembrolizumab is the only drug to achieve a statistically significant DFS benefit vs placebo in a randomized, phase III adjuvant study for high risk, localized RCC.

Answer: False

Aim: Be able to identify differences in the efficacy outcomes between adjuvant sunitinb and adjuvant pembrolizumab for localized RCC patients.

Rationale: The TKI sunitinib showed a significant DFS benefit vs placebo in the S-TRAC trial that led to FDA approval of adjuvant sunitinib for RCC in 2017. However, the S-TRAC trial never showed a survival benefit for sunitinib-treated patients. Whereas, adjuvant pembrolizumab has been associated with statistically significant DFS and OS benefit vs placebo in a similar patient population.

References:

- Motzer, RJ. et al. Adjuvant Sunitinib for High-risk Renal-Cell Carcinoma After Nephrectomy: Subgroup Analyses and Updated Overall Survival Results. EuropeanUrol (2018) 73:62-68.
- Choueiri, TK et al. Overall Survival with Adjuvant Pembrolizumab in Renal-Cell Carcinoma. N Engl J Med (2024) 390:1359-1371.

Question 3: Which of the following regimens is not FDA approved for the first-line treatment of advanced or metastatic (clear cell) renal cell carcinoma?

A) Nivolumab plus Ipilimumab
B) Pembrolizumab plus axitinib
C) Avelumab plus axitinib
D) Nivolumab plus cabozantinib
E) Pembrolizumab plus lenvatinib
F) All are FDA approved regimens

Answer: **F**, all 5 of the two-drug regimens are FDA approved for first-line treatment of advanced or metastatic RCC.

Aim: Recognize an important difference for OS outcome among the 5 FDA approved front-line doublet regimens for advanced RCC

Rationale: The pivotal phase III study with the avelumab plus axitinib regimen (JAVELIN Renal 101) had a positive outcome based on a primary endpoint of PFS (for PDL1 positive tumors) but has never shown a statistically significant survival advantage versus the comparator, sunitinib (final OS analysis presented at ASCO 2024). Whereas, the other four regimens have shown a significant OS benefit vs the same comparator. Therefore, the avelumab plus axitinib regimen, despite its FDA approval in 2019, does not appear in NCCN guidelines as a first-line Preferred Regimen (for clear cell histology).

References:

- Motzer, RJ et al. Avelumab + axitinib vs sunitinib in patients (pts) with advanced renal cell carcinoma (aRCC): Final overall survival (OS) analysis from the JAVELIN Renal 101 phase 3 trial. J Clin Oncol (2024) 42:suppl 16; abstr 4508
- NCCN Kidney Cancer Guidelines v1.2026

Prostate Cancer : Hiba Khan, MD, MPH

Question 1: A patient with metastatic castration-resistant prostate cancer presents for follow up. After presenting with metastatic prostate cancer, he has been maintained on abiraterone acetate and leuprolide. He now complains of worsening hip pain. CT and bone scan reveal progressive metastatic disease, with new osseous metastasis corresponding to the site of his pain. Prior germline sequencing revealed a pathogenic BRCA2 alteration.

You should recommend:

A) Enzalutamide
B) Sipuleucel-t
C) Apalutamide
D) Pembrolizumab
E) Olaparib

Answer: E

Rationale: Olaparib is FDA approved for men with metastatic castration-resistant prostate cancer who have previously progressed on either abiraterone or enzalutamide and have a mutation in one of 14 genes involved in homologous recombination repair, including germline alterations in BRCA1/2. The Phase III PROFound study tested olaparib against either enzalutamide or abiraterone in men previously progressing on a novel hormonal agent. This study showed a statistically significant progression free and overall survival benefit in the olaparib arm.

Pembrolizumab is approved for patients with MSI disease or TMB >10. Apalutamide is approved for men with metastatic hormone-sensitive prostate cancer or M0 castration-resistant prostate cancer. Sipuleucel-t is only appropriate in asymptomatic men with castration-resistant prostate cancer.

Question 2: You see a new patient who was recently diagnosed with metastatic prostate cancer that has spread to his liver, bones and lymph nodes. He initiated on leuprolide 1 month ago and now presents to discuss additional treatment options. He has a history of a seizure disorder but is otherwise a fit 65 year-old man with no additional comorbidities.

What additional therapies should he consider:

A) Cabazitaxel
B) Enzalutamide
C) Darolutamide + docetaxel
D) Apalutamide
E) Lutetium-177 PSMA 617

Answer: C

Rationale: The ARASENS trial established a survival benefit with darolutamide plus docetaxel in men with metastatic hormone-sensitive prostate cancer. Given that he has a seizure disorder, neither enzalutamide nor apalutamide would not be appropriate, as there medications are associated with increased risk for seizures. Darolutamide monotherapy is not approved for metastatic hormone-sensitive prostate cancer. Cabazitaxel is only approved post-docetaxel progression.

Bladder Cancer : Rosa Nadal Rios, MD, PhD

Question 1: 73 yo man presents with 3 month hx of intermittent hematuria and frequency. CT scans of the CAP show thickening of the left bladder wall, no LN, or visceral mets. Pathology confirms a muscle invasive high-grade transitional cell urothelial carcinoma. There is a 3cm mass visualized on EUA. Labs showed an eGFR of 54 mL/min. What do you do next?

What do you do next?

A) Begin intra-vesical therapy with BCG
B) Schedule a cystoprostatectomy with lymph node dissection.
C) Begin systemic perioperative immunotherapy with cisplatin-based combination chemotherapy
D) Start pembrolizumab

Answer: C

Rationale: Perioperative immunotherapy with cisplatin-based combination chemotherapy is one of the the standard of care treatment for muscle-invasive urothelial carcinoma (cT2-4,cN0-N1) based on the results of the NIAGARA trial

BCG and pembrolizumab are used in NMIBC. Single-agent pembrolizumab can also be used in the metastatic setting.

SWOG Intergroup Trial established role for NAC before RC. 5-yr survival for surgery alone 43% vs. NAC + RC 57%

Note: no role for carboplatin in the neoadjuvant setting.

Question 2: A 65 yo man was diagnosed with a cT2N0 bladder cancer, treated with neoadjuvant chemo (ddMVAC) and had ypT3bN+ disease at surgery. NGS confirmed FGFR3 activating mutation. You recommend:

A) Adjuvant nivolumab
B) Adjuvant erdafitinib
C) Adjuvant pembrolizumab
D) Enfortumab vedotin + pembrolizumab

Answer: A

Rationale: Since the patient previously received neoadjuvant chemotherapy and ypT3bN+ disease, he is at high-risk for recurrence. Adjuvant nivolumab is currently FDA-approved therapy in this setting. Erdafitinib is approved in the 2nd line setting of for patients w/ FGFR3 activating mutations in the locally adv / metastatic setting. Adjuvant cisplatin-based chemotheray is not indicated in patients who have received neoadjuvant cisplatin-based chemotherapy. This would be an appropriate treatment for this patient further down the line. EV/pembro is new SOC in 1st line locally adv / metastatic setting.

Hepatocellular Cancer : William P. Harris, MD

Question 1: A 67 year-old woman is found to have multifocal HCC, peritoneal metastases and a biopsy proven adrenal metastasis. ECOG performance status is 1 and the patient has Child Pugh A cirrhosis (radiographically evident) secondary to prior Hepatitis C and evidence of splenomegaly on examination. She had an upper GI bleed 2 months ago which has resolved. The patient has no significant additional comorbidities.

What is the next step in patient care:

A. Perform EGD prior to planned atezolizumab/bevacizumab
B. Initiate sorafenib
C. Initiate single dose tremelimumab + ongoing durvalumab
D. Refer to palliative care
E. Refer for treatment of hepatitis C

Answer: C

Rationale: While Atezolizumab/bevacizumab or Single dose Tremelimumab + durvalumab are both optimal 1st line options and superior to sorafenib, in this case the recent GI bleed favors the Durvalumab/tremelimumab. Given the patient has good functional status and Child Pugh A cirrhosis, treatment is indicated. The benefit of treatment of hepatitis C in advanced disease remains unclear but systemic therapy for HCC is clearly the priority.

Reference: Finn et al. NEJM 2020 382:1894-1905; Abou-Alfa GK et al. Future Oncol 2023 Sep 6. Epub ahead of print. PMID: 37671641

Question 2: A 62 year-old man with a 3 year history of HCC has undergone prior RFA, TACE and radiation segmentectomy but now has extensive multifocal disease progression. ECOG performance status is 2. The patient has refractory ascites, encephalopathy, and Child Pugh C cirrhosis without a clearly reversible process. Transplantation is not an option.

The next most appropriate step in therapy is:

A. Initiate systemic therapy
B. External beam radiation
C. Referral for surgery
D. Bilateral lobar Y90
E. Referral to palliative care/hospice

Answer: E

Rationale: Patients with Child Pugh C cirrhosis could be considered for very selective interventions, although typically to downstage to transplant candidacy. Systemic therapy has not demonstrated benefit in patients with Child Pugh C cirrhosis and could cause harm. Referral to palliative care and likely hospice enrollment is indicated.

Reference: EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. Mar 2012 *Eur J Cancer* 48(5) pp599-641

Tuesday, October 7

Non-Small Cell Lung Cancer - Adjuvant/Locally Advanced : Rafael Santana-Davila, MD

Question 1: In the treatment of locally advanced lung cancer immunotherapy with durvalumab should be considered to start.

A) Two weeks after finishing concurrent chemo radiation.
B) After consolidation chemotherapy has been done.
C) After the first restaging CT scan to make sure there is no pneumonias.
D) No role for immunotherapy in this setting.

Answer: A

Question 2: A patient undergoes resection for a stage IIIA lung cancer. She is found to have an EGFR L858R mutation. Is referred to oncology by surgery, the recommendation is.

A) Osimertnib is the is the new current standard of care instead of chemotherapy in the adjuvant setting.
B) Osimertinib has not role and should not be considered unless in the context of a clinical trial.
C) Should be considered after adjuvant chemotherapy.
D) Should be done concurrently to chemotherapy.

Answer: C

Non-Small Cell Lung Cancer - Metastatic : Christina S. Baik, MD, MPH

Question 1: A 62 year old man presented with back pain and was found to have a metastatic lesion in the L3 vertebral body without evidence of cord impingement on MRI. Biopsy showed metastatic squamous cell carcinoma with no PD-L1 expression by immunohistochemistry. CT scans of the chest, abdomen, and pelvis showed a bulky left hilar mass with bilateral mediastinal lymphadenopathy, as well as additional metastatic lesions in the left clavicle and right 8th rib. He completed palliative radiation to the L3

metastasis with good improvement of his pain. He has a non-productive cough and a 5 kg weight loss over the past 2 months. His ECOG PS is 1.

Which is the most appropriate selection for first-line therapy?

A) Pembrolizumab
B) Carboplatin and pemetrexed and pembrolizumab
C) Carboplatin and paclitaxel and bevacizumab
D) Carboplatin, paclitaxel and pembrolizumab
E) Docetaxel and ramucirumab

Answer: D

Rationale: A is incorrect as pembrolizumab monotherapy has not been shown to be superior to platinum doublet chemotherapy in patients whose tumor lacks PD-L1 expression. B is incorrect as pemetrexed based chemotherapy has been shown to be inferior to gemcitabine based therapy in squamous histology, and currently is FDA approved for non-squamous histology (Scagliotti JCO 2008). C is incorrect as bevacizumab is contraindicated in squamous histology (Sandler NEJM 2006). In the original trial that led to the approval of bevacizumab as first-line therapy for NSCLC, patients with squamous cell histology were excluded due to the observed increased risk of life threatening hemoptysis in earlier trials. Docetaxel and ramucirumab combination have shown to be active in patients who progressed on a platinum doublet chemotherapy (Garon Lancet 2014). Patients with metastatic squamous cell lung cancer who have acceptable performance status and comorbidities should receive a platinum doublet chemotherapy in combination with an immune checkpoint inhibitor if their tumoral PD-L1 expression is negative, rather than chemotherapy alone. In KEYNOTE-407, triplet therapy with carboplatin, taxane (paclitaxel of nab-paclitaxel) and pembrolizumab resulted in superior survival compared to chemo alone (Paz-Ares et al. NEJM 2018). This regimen was FDA approved in the fall of 2018.

Question 2: A 70 year old woman with remote smoking history is found to have a LLL lung mass on a routine CXR obtained prior to an elective cholecystectomy. Biopsy of the lung mass reveals a TTF-1 positive adenocarcinoma and subsequent PET imaging shows FDG avid mediastinal nodes, small liver lesions and a left adrenal mass. Biopsy of the left adrenal mass confirmed the same adenocarcinoma. Molecular and PDL1 testing show that her tumor harbors EGFR deletion 19 mutation and 90% PD-L1 expressed.

What is the next best step?

A) Pembrolizumab
B) Carboplatin and pemetrexed
C) Osimertinib
D) Osimertinib and pembrolizumab
E) Erlotinib and pembrolizumab
F) Osimertinib plus carboplatin/pemetrexed
G) C or F

Answer: G

Rationale: This patient has EGFR oncogene driven lung cancer with high PD-L1 expression. Multiple trials of immune checkpoint inhibitor (ICI) therapy have shown that patients with EGFR mutation positive NSCLC have a low likelihood of clinical benefit, even in those with high PDL1 expression (Lisberg JTO 2018, Garon NEJM 2015). A randomized trial of carboplatin/ pemetrexed vs carboplatin/pemetrexed and pembrolizumab in patients with EGFR del 19 or L858R mutation showed that the addition of pembrolizumab was not beneficial (KEYNOTE-789, Yang JCO 2024). First line treatment in EGFR mutation positive NSCLC should be an EGFR tyrosine kinase inhibitor regardless of the PDL1 status. Osimertinib is a third generation EGFR TKI that is active against the resistance mutation T790M and has shown to result in superior PFS compared to erlotinib / gefitinib in treatment naïve patients, thus has become a preferred agent in the first line setting (FLAURA, Soria NEJM 2018). Recent study combining osimertinib and chemotherapy showed improved PFS when compared to osimertinib (FLAURA2, Planchard NEJM 2023), however, it is unknown whether upfront combination therapy is superior to sequential. Thus both options are reasonable as first line therapy. B is incorrect since TKI therapy has shown clear superiority over platinum doublet in multiple randomized trials among EGFR mutant patients. D and E are incorrect since there is no robust safety or efficacy data for the combination of TKI and immune checkpoint inhibitor. In fact, severe toxicities have been observed in early trials of this combination, resulting in early closure of some of these trials (Schoenfeld Ann Oncol 2019)

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Mesothelioma : Nicholas P. Giustini, MD

Question 1: A 70 year-old male with a history of HTN, COPD, afib c/b thromboembolic CVA 2 months prior on rivaroxaban, presents with a new diagnosis of unresectable epithelioid malignant pleural mesothelioma. Which of the following would NOT be an acceptable first line therapy?

A. Cisplatin + pemetrexed
B. Cisplatin + pemetrexed + bevacizumab
C. Carboplatin + pemetrexed + pembrolizumab
D. 4Ipilimumab + nivolumab

Answer: B

Rationale: Cisplatin + pemetrexed + bevacizumab (answer B) would not be a recommended first line therapy in this patient with a recent CVA. All other options (answers A, C, and D) would be acceptable choices.

Question 2: Which of the following is FALSE?

A. Cisplatin + pemetrexed is the regimen of choice for both the neoadjuvant and adjuvant settings in resectable mesothelioma.
B. It is preferred to include checkpoint inhibitor therapy when treating first line metastatic biphasic mesothelioma.
C. Somatic BAP1 mutations are associated with improved prognosis in mesothelioma.
D. It is unclear whether EPP or P/D is considered a superior surgical oncologic approach in pleural mesothelioma.

Answer: C

Rationale: Germline BAP1 mutations are associated with improved prognosis in mesothelioma. While somatic BAP1 mutations (answer C) are more common, there has not been a demonstrated association with overall survival benefit. When surgery is considered, the standard of care for neoadjuvant or adjuvant therapy is cisplatin + pemetrexed (answer A). The use of checkpoint inhibitor therapy (immunotherapy) is preferred for unresectable non-epithelioid (biphasic or sarcomatoid) mesothelioma (answer B) in patients without contraindications to immunotherapy. Robust data do not exist showing EPP or P/D as a superior surgical oncologic approach (answer D) though EPP is considered more morbid.

Melanoma and other Skin Cancers : Shailender Bhatia, MBBS

Question 1: A 75-year-old man presents with progressive anorexia, weight loss, night sweats, fatigue and right-sided abdominal pain for the last few weeks.

Imaging studies show widely disseminated metastases in multiple organs, including greater than 50% liver involvement. Brain MRI shows 5 brain metastases (largest was 1.5 cm in R-frontal lobe); he denies neurologic symptoms and neurologic examination was unremarkable.

Biopsy of a liver tumor reveals metastatic melanoma with BRAF V600E mutation present.

Laboratory analyses reveal Hemoglobin 10, AST 75, ALT 85, ALK-P 375 and Bilirubin 1.8. His ECOG performance score is 2.

What will you recommend next?

A. Whole brain radiation therapy (WBRT)
B. Anti-PD-1 monotherapy (pembrolizumab or nivolumab)
C. Combination immunotherapy (Ipilimumab-nivolumab or relatlimab-nivolumab)
D. BRAFi plus MEKi
E. Hospice

Answer: D

Rationale: This patient has impending hepatic failure due to progressive liver metastases. To stabilize his situation, urgent and reliable tumor regression is needed, which is best provided by BRAF-targeted therapy.

A. WBRT is seldom used for upfront treatment of metastatic melanoma with brain metastases, as systemic therapy offers the best chance of disease control both intra- and extra-cranially. WBRT is mostly reserved for short term palliative benefit in the absence of effective systemic therapy options.
B. While PD-1 monotherapy can be effective, ORR is only around 40% and it is not possible to predict a response. Also, the kinetics of tumor regression with immunotherapy can sometimes be slow, which will put this patient at high risk of decompensation.
C. In most metastatic melanoma patients with BRAF V600 mutant melanoma, who don't have bulky, threatening metastatic burden, combination immunotherapy is now preferred over BRAFi+MEKi, as it offers the best chance of long-term outcomes (as shown in DREAMSEQ trial). However, similar to option "b", in this patient with impending hepatic failure, while the ORR with combination such as Ipi-Nivo is higher than PD-1 monotherapy (around 55% for Ipi-Nivo), it is not possible to predict a response. Also, the kinetics of tumor regression with immunotherapy can sometimes be slow, which will put this patient at high risk of decompensation. If this patient had melanoma without BRAF V600 mutation, combination IO will be the preferred option, although tumor regression will be unpredictable.
D. Since BRAF V600 mutation is present, BRAFi+ MEKi is the preferred option here due to the high rate (~95%) of tumor regression with BRAFi+MEKi (primary/intrinsic resistance is seen in only ~5% of patients). Also, due to the quick onset of regression (typically within days), this therapy will have the best chance of rapid symptom palliation and tumor control, allowing reversal of hepatic dysfunction. BRAFi+MEKi is also associated with intra-cranial responses, hence offering a high chance of addressing brain metastases too, without requiring radiation therapy. Since responses with BRAFi+MEKi are not likely to be highly durable (median PFS in brain metastases is ~ 4 months), proactive switching after ~2 months to immunotherapy (preferably a combination regimen such as Ipi-Nivo) is recommended to try for achieving durable control (this proactive switching strategy has been tested prospectively in the SECOMBIT trial with outcomes appearing better than targeted therapy continued till progression).

NOTE: Triple combination of BRAFi+MEKi+anti-PD-1 may be another acceptable option here. In the IMSPIRE-150 trial, the triple combination was associated with improved PFS as compared to BRAFi+MEKi. However, with triple combination, it is challenging to attribute toxicities to BRAFi-MEKI vs immunotherapy, and there is a possibility of over-treatment of toxicities with steroids.

Unless a patient is not at all interested in receiving anti-cancer treatment, hospice is not a reasonable first choice here, given the possibility of durable disease control and long-term survivorship with successful use of the existing treatment choices for metastatic melanoma.

Question 2: A 27-year-old woman with newly diagnosed metastatic melanoma (with BRAF V600 mutation) with asymptomatic, pulmonary metastases has received 2 doses of ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) recently. She is in clinic to discuss the results of her restaging radiologic studies performed at 6 weeks after initiation of therapy.

The imaging studies show an increase in the size of two pulmonary nodules (1.5 to 2 cm and 1.2 to 1.8 cm, respectively) and interval development of a new 0.8 cm nodule, as compared to the baseline scans. There are no other new sites of disease.

She is asymptomatic except grade 1 pruritus and skin rash that started after the first dose.

What would you recommend next?

A. Start Ipilimumab at 10 mg/kg
B. Switch to Nivo 3 mg/kg plus Ipi 1 mg/kg
C. Continue Ipi-Nivo at current dose and repeat imaging in 4-6 weeks
D. Switch to BRAFi_MEKi

Answer: C

Rationale: While the restaging scan suggests possible progressive disease at this early timepoint of 6 weeks, the increase in size of pulmonary nodules is small and non-threatening and could represent 'pseudo-progression' due to inflammatory swelling of the tumors. Hence, continued observation to see maturation of the anti-tumor immune response with the current regimen is the preferred choice here.

a. High-dose ipilimumab (10 mg/kg) was FDA-approved for adjuvant treatment of high-risk melanoma but is no longer used in melanoma treatment due to high toxicity rates without much additional benefit over standard-dose Ipilimumab (3 mg/kg). In the setting of metastatic melanoma, Ipi-Nivo combination has much higher response rates than ipilimumab alone.
b. Ipi3-Nivo1 and Ipi1-Nivo3 were compared in the Checkmate 511 trial and found to have similar efficacy outcomes. Numerical response rate (as well as toxicity) were higher in the Ipi3-Nivo1 arm, suggesting stronger immune activation with this regimen. Hence, switching to Ipi1-Nivo3 is unlikely to reverse melanoma progression, if that were the underlying reason for radiologic findings.
c. Immune-mediated anti-tumor responses can take several weeks to mature. In earlier trials of ipilimumab,12-16 weeks was the median time to response and pseudo-progression was not uncommon. A significant proportion of patients with ipi-nivo combination also have responses in this time frame. Given that the apparent progression seen in this patient at 6 weeks is mild and clinically non-threatening, it will be reasonable to continue treatment and obtain restaging evaluation in a few weeks after the 4th and final dose. If major progression were noted at 6 weeks, then consideration could be given to switching therapy to an alternative regimen, such as BRAFi-MEKi to prevent clinical deterioration.
d. While BRAFi-MEKi could be used, immunotherapy offers the best possible long-term outcomes for this patient. Since the apparent progression is mild and not clinically threatening, it is appropriate to wait and see the final response to Ipi-Nivo before switching therapies.

Question 3: 42-year-old man presented with 3.4 mm thick, ulcerated primary melanoma (pT3b) located on the right arm. Wide local excision revealed no residual melanoma and sentinel lymph node biopsy showed 1 of 1 axillary lymph node involved with metastatic melanoma (size of deposit 5 mm) (pN1a). Staging FDG-PET scan and brain MRI did not show any metastatic disease. BRAF testing of the primary tumor was negative for the presence of BRAF V600E mutation.

What is the most appropriate next step in treatment?

A. Completion axillary lymph node dissection
B. Adjuvant radiation therapy to the right axillary basin
C. Adjuvant systemic therapy with nivolumab or pembrolizumab
D. Adjuvant systemic therapy with ipilimumab plus nivolumab

Answer: C

Rationale: This patient has resected stage IIIC (pT3bpN1a) melanoma with a high risk of systemic recurrence and mortality.

a. & b) While surgery and adjuvant radiation were historically used to reduce the loco-regional recurrence risk in such patients, these did not lead to substantial improvement in melanoma-specific survival (e.g. MSLT-2 trial).
c. Nivolumab and pembrolizumab are FDA approved for adjuvant therapy for patients with resected stage III melanoma (as well as resected high-risk stage IIB and IIC too). These agents have led to consistent improvement in relapse-free survival and other efficacy endpoints in several phase 3 trials in high-risk melanoma patients. A discussion of adjuvant systemic therapy is reasonable in all high-risk patients with final choice guided by patient preference for improving outcomes versus tolerance for toxicity.
d. Ipilimumab (1 mg/kg every 6 weeks) plus nivolumab was compared to nivolumab monotherapy in resected stage III melanoma patients, but did not improve efficacy and expectedly had greater toxicity in the adjuvant setting. However, recent neo-adjuvant trials (including NADINA) have revived the role of combination ICI in earlier stages of melanoma.

Head, Neck and Thyroid Cancer : Lauren C Shih, MD

Question 1: A 35 year old male patient of Southern Chinese descent presents with a 6 month history of left sided middle ear effusions refractory to empiric antibiotics. CT imaging of the head and neck confirms the presence of a mass in the left Fossa of Rosenmuller invading bone. Biopsy of the nasopharyngeal mass showed a WHO grade III undifferentiated carcinoma, EBER positive. Staging shows no evidence of distant disease or nodal involvement. He has a PS of 0 and no significant co-morbidities.

Which of the following is true regarding the treatment recommendation for this patient:

A. The treatment goal is cure, and definitive radiotherapy combined with concomitant cisplatin followed by adjuvant cisplatin and 5-FU is an appropriate recommendation
B. The treatment goal is cure and debulking surgery followed by adjuvant radiation therapy is an appropriate recommendation
C. The treatment goal is palliation and systemic chemotherapy alone with gemcitabine and cisplatin is appropriate.
D. The treatment goal is palliation and referral to hospice and palliative care is appropriate.
E. The treatment goal is cure, and definitive radiation in combination with cetuximab is an appropriate recommendation.

Answer: A

Rationale: This gentleman has endemic nasopharyngeal cancer, with tumor often arising from the Fossa of Rosenmuller causing Eustachian tube dysfunction/obstruction frequently manifesting as middle ear effusions in adults. These patients often present with locally advanced disease, and are candidates for curative intent therapy. The standard therapy for poorly differentiated, endemic NPC is the administration of concomitant cisplatin based chemotherapy with radiation, established by the landmark North American Intergroup 0099 trial (Al-Sarraf, JCO PMID 9552031). The dose of radiotherapy is 70Gy to the primary and involved cervical nodal areas followed by adjuvant cisplatin/5FU). Randomized data from endemic areas have called into question the need for adjuvant therapy, but these trials have not been replicated in the North American population. There is no role for debulking surgery or cetuximab as a curative therapy for this subtype of H&N cancer.

A recent clinical trial in endemic nasopharyngeal carcinoma (Zhang et al NEJM 2019 PMID: 31150573) also supports a survival benefit to induction chemotherapy followed by definitive radiation therapy in patients who have a heavy nodal disease burden (Stage III/IV).

Question 2: You evaluate a 68/M following curative intent surgery for a T3 oral cavity squamous cell carcinoma. He is a former alcoholic and active smoker. His pathology showed negative surgical margins at the primary site, and 2 out of 37 cervical lymph nodes contained malignancy, the pathology report describes extra-capsular extension in the largest lymph node measuring 2.8 cms. The patient recovered well from surgery, has no significant co-morbidities and a PS of 0. You would recommend:

A. Adjuvant radiation therapy with concurrent cisplatin chemotherapy
B. Observation, no additional therapy
C. Cetuximab concurrent with radiotherapy
D. Adjuvant chemotherapy with three cycles of cisplatin, docetaxel and 5-FU
E. Radiotherapy alone

Answer: A

Rationale: This patient has a pT3 N2b (metastasis in multiple ipsilateral LNs, none > 6 cm), Stage IVA oral cavity squamous cell carcinoma, high risk pathologic features (extracapsular spread). Two landmark randomized clinical trials (from the RTOG: Cooper NEJM 2004 PMID 15128893; and the EORTC: Bernier NEJM 2004 PMID 15128894) compared cisplatin concurrent with radiation to radiation alone in patients with high risk resected squamous cell carcinomas of the head and neck. These both demonstrated improved progression-free survival and loco-regional control in patients with high risk features, the EORTC demonstrated an overall survival benefit to chemoradiation (not statistically significant in the RTOG trial). Although these trials had slightly different inclusion criteria, a combined analysis showed that patients with positive surgical margins or extranodal tumor extension had a clear benefit from the addition of chemotherapy.

Question 3: A 56 year old male, active smoker presents with hoarseness, dysphagia and aspiration. An evaluation revealed a large tumor originating from the left supraglottic larynx, with radiographic evidence of thyroid cartilage invasion. A biopsy of this tumor revealed a moderately differentiated squamous cell carcinoma. A full staging evaluation revealed the laryngeal mass, as well as bilateral necrotic cervical lymph nodes. There was no evidence of distant metastases. He has no significant comorbidities, and has a PS of 1. You present him at the multidisciplinary clinic and recommend:

A. Palliative care and hospice
B. Larynx preservation with cisplatin 100mg/m2 on days 1,22 and 43 concurrent with radiotherapy
C. Larynx Preservation using cetuximab one week prior to radiotherapy and continued weekly concurrent with radiotherapy
D. Upfront laryngectomy and bilateral neck dissection with postoperative therapy directed by pathologic features of the resected specimen
E. Induction chemotherapy with three cycles of cisplatin, 5-FU, docetaxel followed by radiation therapy

Answer: D

Rationale: This patient is a poor candidate for an organ preserving approach due to a T4 tumor with frank extralaryngeal extension. These patients were excluded from RTOG 99-11, the landmark clinical trial that established cisplatin based chemoradiation in patients with larynx cancer (Forastiere NEJM, 2003 PMID 14645636). Patients with extralaryngeal extension are best treated with curative intent with upfront surgical resection and reconstruction followed by adjuvant therapy.

Question 4: A 45 year old patient undergoes larynx preservation for a T3N2b M0 squamous cell carcinoma of the glottis with concomitant chemoradiation. A reevaluation of her disease at 12 weeks after completion of therapy reveals biopsy proven persistent disease in the larynx and residual pathologically enlarged neck lymph nodes. CPS is 0. The patient has a PS of 0 and is interested in additional therapy, if one is available. At this point you would recommend:

A. Refer back surgery for consideration of salvage resection
B. Initiate carboplatin, 5-FU and pembrolizumab
C. Start palliative chemotherapy cetuximab, carboplatin, 5-FU
D. Start palliative carboplatin and gemcitabine
E. Refer the patient back to radiation oncology and consider repeating radiotherapy, but this time in combination with cetuximab

Answer: A

Rationale: This patient has residual disease despite platinum and radiation therapy and it is appropriate to evaluate her for salvage laryngectomy. Unlike other primary sites in the head and neck, salvage surgical resection is often successful in patients with larynx cancer who fail organ preservation strategies(Weber 2003 Arch Otol Head Neck Surg PMID:12525193).

Question 5: You treated a 58/M with a T3 N2c M0 p16+ oropharynx squamous cell carcinoma with cisplatin based chemoradiation. He develops biopsy proven evidence of lung metastases 1 year later, with CPS of 50. He has a PS of 0 with minimal comorbidity. Which of the following is true regarding his treatment options:

A. His chances of responding to immune checkpoint inhibition are improved by his p16+ status
B. Pembrolizumab monotherapy is associated with improved overall survival
C. The combination of pembrolizumab, platinum and 5-FU has low rates of high grade treatment related toxicities
D. Palliative chemotherapy with cetuximab, platinum and 5-FU is appropriate.
E. Genetic testing for activating EGFr mutations should be obtained, and cetuximab initiated if testing is positive.

Answer: B

Rationale: The Keynote-48 trial (Burtness et al. Lancet 2019 PMID: 31679945) enrolled patients previously untreated in the first line R/M setting, showed a survival benefit to pembrolizumab alone in PDL1 expressing (CPS > or =1) and pembrolizumab +platinum + F5U (regardless of CPS status), compared to the EXTREME regimen (cetuximab+platinum + 5FU). Pembrolizumab monotherapy is approved as first line therapy in the CPS positive patients, and pembrolizumab + platinum +5-FU is approved for first line therapy in all comers regardless of CPS. The combination of pembrolizumab+platinum + F5U is associated with >70% grade 3 or higher toxicity.

Question 6: Regarding HPV related oropharynx squamous cell carcinomas the following statements are true, **except:**

A. p16 IHC is an adequate method to establish HPV positivity
B. The incidence of HPV oropharyngeal cancer has increased in the last decade
C. The cure rates for locally advanced, HPV positive, oropharynx cancers are higher than in HPV negative tumor matched by stage
D. The most common HPV subtype detected in these tumors is HPV 18
E. The use of HPV vaccine may decrease HPV related oropharynx cancer

Answer: D

Rationale: Positive p16 immunohistochemical staining is a reliable surrogate for the presence of HPV genomic integration in tumor cells among patients with HPV related oropharynx cancer. Analysis of clinical trial data has shown that HPV related oropharynx cancers show improved response to treatment and better survival when compared to patients having HPV negative oropharynx tumors when matched by stage. Incidence of HPV related oropharynx cancers has increased over the past 3 decades. Greater than 90% of these tumors are related to HPV subtype 16.

Question 7: A 58 year old woman is fatigued and presents for exam. On physical examination the liver edge is palpable 2.5cm below the right costal margin. An ultrasound is performed findings multiple liver lesions. A CT scan of the chest, abdomen and pelvis is performed and finds a mass in the thyroid gland and multiple liver lesions. CEA is elevated 14. A colonoscopy is negative. A biopsy of the liver lesion is performed and is consistent with medullary thyroid carcinoma. You recommend meeting with a genetic counselor, and recommend

A. Erlotinib
B. RET mutational testing and RET directed TKI
C. Cisplatin and Fluorouracil
D. Radioactive Iodine
E. Supportive care alone, since no systemic agents have activity in this disease

Answer: B

Rationale: Medullary thyroid cancers are neuroendocrine tumors of the thyroid parafollicular cells, these are rare malignancies and can be a manifestation of inherited cancer syndromes (MEN). Sporadic medullary thyroid cancers usually harbor a sporadic RET mutation, patients with familial disease often will have a germline mutation in RET. These do not concentrate iodine and often elaborate calcitonin and CEA. Primary treatment is surgical resection when feasible. Randomized placebo controlled trials in patients with metastatic medullary thyroid cancers have led to the approval of two oral tyrosine kinase inhibitors (TKIs) for this disease: vandetanib (Wells JCO 2013 PMID: 22025146) and cabozantinib (Elisei JCO 2014 PMID: 2400250), which both demonstrated superior progression free survival with TKI therapy. Patients who harbor a RET fusion mutation are also candidates for the RET specific TKI selpercatinib (Wirth et al. NEJM 2020 PMID: 32846061) which is FDA approved. The FDA approval for pralsetinib in MTC was withdrawn in July of 2023.

Question 8: A 40 year old woman presents to her primary care provider with a cough. She underwent a thyroidectomy 6 years ago for a papillary thyroid cancer after which she received radioactive iodine and then no further treatment or surveillance because she moved out of the area. A chest radiograph shows multiple lung nodules. A CT scan with PO and IV contrast is performed and confirms these findings. Serum thyroglobulin is measures and is elevated at 195 ng/ml. A diagnostic radioactive iodine scan is performed and reveals no evidence of disease.

What is the next step in management?

A. Surgical resection of visible disease
B. Radioactive Iodine Treatment
C. Initiation of the tyrosine kinase inhibitor lenvatinib
D. Adriamycin
E. Cyclophosphamide, adriamycin and vincristine

Answer: B

Rationale: The patient has recurrent metastatic disease of thyroid cancer and the treatment of choice is radioactive iodine. Her iodine body scan was performed after a CT scan with contrast which chronileads to a false negative result. Lenvatinib and sorafenib are both approved for radioactive iodine refractory thyroid carcinomas. In general thyroid malignancies are chemotherapy insensitive.

Sarcoma : Min S Park, MD, MS

Question 1: A patient with dedifferentiated liposarcoma of the thigh was treated with 6 cycles of neoadjuvant doxorubicin 75 mg/m^2 and ifosfamide 10g/m^2 followed by radiation and surgery. One year later he develops metastatic disease and is seen in your office after progressing on gemcitabine 900 mg/m^2 and docetaxel 75mg/m^2.

Which is the best next systemic treatment?

A. Doxorubicin
B. Pazopanib
C. Dacarbazine
D. Tazemetostat
E. Trabectedin

Answer: E

Rationale: Trabectedin is approved for metastatic dedifferentiated liposarcoma based on a PFS benefit over dacarbazine (PMID: 26371143). The patient has already received 450mg/m^2 doxorubicin so additional anthracycline should be avoided if other options exist due to the potential for cardiotoxicity. Pazopanib is not approved for liposarcoma. Dacarbazine was the comparator arm in the trial supporting trabectedin. Tazemetostat is an EZH2 inhibitor approved for epithelioid sarcoma, not liposarcoma.

Question 2: A patient with metastatic gastrointestinal stromal tumor is started on 400 mg imatinib daily shortly after diagnosis. You concurrently order mutation testing and the result returns with a KIT exon 9 mutation.

What is the best next step in management?

A. Continue imatinib 400 mg PO daily
B. Increase imatinib to 800 mg PO daily
C. Switch to Sunitinib 50 mg PO 4 weeks on, 2 weeks off
D. Switch to Pazopanib 800 mg daily

Answer: B

Rationale: Patients with KIT exon 9 mutations benefit from higher doses of imatinib (PMID: 16624552). Sunitinib is the standard second line therapy after progression or intolerance on imatinib (PMID: 17046465). Pazopanib is a tyrosine kinase inhibitor approved for use in non-adipocytic soft tissue sarcomas (PMID: 22595799).

Small Cell Lung Cancer : Molly Tokaz, MD

Question 1: Which of the following is TRUE regarding management of limited stage small cell lung cancer?

A. Prophylactic cranial irradiation should be offered to all patients with a demonstrated response to chemoradiation.
B. Mediastinal staging is recommended only for patients with tumors <7 cm and clinically node negative.
C. There is never a role for resection of limited stage small cell lung cancer.
D. Patients can have limited stage disease even if a pleural effusion is present.

Answer: A

Rationale: Prophylactic cranial irradiation should be offered to all patients with limited stage small cell lung cancer with response to chemoradiation given a demonstrated overall survival benefit and decreased incidence of brain metastases. Answer (b) is incorrect, as mediastinal staging should be considered for **tumors <5 cm** and clinically node negative as these are patients who for whom you consider resection (if confirm pathologically node negative). Answer (c) is incorrect because resection is considered for T1-2 (tumor <5 cm) pN0 disease. The presence of a pleural effusion is consistent with extensive stage disease, making answer (d) incorrect.

Question 2: A 56-year-old female patient with extensive stage small cell lung cancer presents to your office. She completed 4 cycles of carboplatin/etoposide/durvalumab with good treatment response, and has now been on maintenance durvalumab for 2 months. Unfortunately, her restaging CT scan shows worsening mediastinal lymphadenopathy and new osseous metastases. She has a good performance status, no significant laboratory abnormalities, and would like to continue receiving treatment. **All of the following would be a reasonable next step, EXCEPT:**

A. Lurbinectedin
B. Topotecan
C. Tarlatamab -dlle
D. Paclitaxel
E. Carboplatin/etoposide

Answer: E

Rationale: Carboplatin/etoposide rechallenge is not recommended because your patient has experienced disease progression <3 months from prior carboplatin/etoposide exposure. Lurbinectedin, topotecan, or paclitaxel would all be reasonable second line treatment options, although only the first three are FDA approved for this indication.

Solid Tumor Pharmacology Pearls : Amy L. Indorf, PharmD, BCOP

Question 1: 54 year old woman with ER+, PR-, HER2 1+ invasive ductal carcinoma with 2 positive lymph nodes s/p lumpectomy and radiation receiving adjuvant docetaxel and cyclophosphamide.

Which of the following are dermatologic adverse effects associated with this regimen?

A) Alopecia
B) Paronychia and onycholysis
C) Macular and papular eruptions
D) Palmar-plantar erythrodysesthesia
E) All of the above

Answer: E

Rationale: ALopecia in almost 100% of patients, and this includes some level of alopecia microtubule targeting agents, vincas, eribulin though to lesser degrees
Paronychia – infection around nail bed friable tissue
Onycholysis – lifting up of the fingernails
Though less common than agents like liposomal doxorubicin and 5FU, taxanes can cause HFS. They can present classical or on the dorsal surfaces and can sometimes present with pain and erythema over the knuckles or joints and be associated with nail changes or lifting of the fingernails as well. Because it's less common, we don't recommend the same up front prevention strategies as with 5FU based therapies or liposomal doxorubicin, but can consider the same management strategies if patients start reporting HFS signs or symptoms.

Question 2: 54 year old woman with ER+, PR-, HER2 1+ invasive ductal carcinoma with 2 positive lymph nodes s/p lumpectomy and radiation receiving adjuvant docetaxel and cyclophosphamide.

Which of the following statements are true regarding alopecia?

A) Minoxidil may help in prevention of hair loss once cytotoxic chemotherapy is initiated
B) Randomized clinical trials show 90% of patients developing grade 1 alopecia with scalp cooling versus 0% without scalp cooling
C) Guidelines do not recommend considering scalp cooling to reduce chemotherapy-induced alopecia
D) Scalp cooling trials show greater efficacy with taxane-based regimens and lower efficacy when anthracyclines are combined with taxane or cyclophosphamide

Answer: D

Rationale:

- Low dose Minoxidil may help in regrowth once cytotoxic chemotherapy has been completed. MInoxidil causes vasodilation and premature entry of the follicles into the growth phase to accelerate hair regrowth. Low dose minoxidil from 1.25mg to 5mg has been used, and the most recent trial I saw used 1.25mg daily and showed increased in frontal hair density and occipatal hair dnesity in ¾ of patients.
- Randomized clinical trials show 50-65% of patients developing grade 1 alopecia with scalp cooling versus 0% without scalp cooling
- Guidelines recommend considering scalp cooling to reduce chemotherapy-induced alopecia
- Scalp cooling can be done via machine based or vasoconstricting caps but the data is with machine based cooling. Guidelines do recommend considering machine based cooling for patients based on the data above. The data is primarily in breast cancer patients and as shown in point 4, most effective with taxane based regimens compared with other drugs, like platinums or antrhacyclines. Newer drug therapies, like our antibody drug conjugates, are allowign machines based scalp cooling per protocol, so we may have more informaton about this in the future. Concern is for rate of scalp metastastes which is comparable to non-scalp cooling arm. Contrindication is in hematologic malignancies

Question 3: 54 year old woman with ER+, PR-, HER2 1+ invasive ductal carcinoma with 2 positive lymph nodes s/p lumpectomy and radiation receiving adjuvant docetaxel and cyclophosphamide.

Which of the following statements are true regarding cutaneous toxicities with taxanes? (Choose all that apply)

A) Macular and popular eruptions tend to occur in flexural areas or intertriginous zones
B) Folliculitis may occur but is not dose-limiting
C) Palmar plantar erythrodysesthesia (hand foot syndrome) is more common docetaxel and distinctly presents on the dorsal surface
D) There is a higher incidence of hand-foot syndrome with taxanes compared to 5-flurouracil based therapies.

Answer: A, B and C

Rationale: HFS most common with liposomal doxorubicin (40-50%) and 5FU based therapies (50-60%)

Question 4: 54 year old woman with ER+, PR-, HER2 1+ invasive ductal carcinoma with 2 positive lymph nodes s/p lumpectomy, radiation, and adjuvant docetaxel and cyclophosphamide x4 cycles. She will be receiving adjuvant CDK 4/6 inhibitor and endocrine therapy with ribociclib and letrozole.

Ten days after initiation, her AST is 75 (2xULN) and her ALT is 195 (5.9xULN). Her Tbili is WNL. What is our next course of action?

A) This is Grade 1 (>ULN to 3xULN) elevation, no changes necessary
B) This is Grade 1 AST elevation and Grade 3 ALT elevation, no changes necessary.
C) This is Grade 2 (3-5xULN), hold ribociclib until recovery to baseline and restart at the same dose
D) This is Grade 3 (5-20xULN), hold ribociclib until recovery to baseline and resume at the next lower dose level

Answer: D

Rationale: Many of our oral TKis can cause transaminitis, usually resolve with withholding the medication. We look at the half-life of the drug and expect resolution of the LFTs within that time. For instance, the half life of ribo is about 32h and we expect that the drug will be out of the body in 3-5 half lives or 4-7 days. We can re-draw LFTs in a week and so whether or not we can safely resume the drug. We can consider f/u LFts 1 week after to see if tehre is recurrence of the transaminitis.

Question 5: 54 year old woman with ER+, PR-, HER2 1+ invasive ductal carcinoma with 2 positive lymph nodes s/p lumpectomy, radiation, and adjuvant docetaxel and cyclophosphamide x4 cycles. She will be receiving adjuvant CDK 4/6 inhibitor and endocrine therapy with ribociclib and letrozole.

Two weeks after initiation, labs show a SCr of 1.1mg/dl. Her baseline SCr is 0.8mg/dl. She denies diarrhea, fever, signs or symptoms of UTI or other infections. She is drinking 8-12 cups of water a day. Which of the following statement best represents management of serum creatinine increase?

A) Abemaciclib is known to increase SCr, continue abemaciclib
B) As all other causes of AKI have been ruled out, hold drug and draw a cystatin C. Resume when cystatin C results show normal GFR
C) As all other causes of AKI have been ruled out, draw a cystatin C and continue abemaciclib.
D) Abemaciclib is renally cleared, hold the medication until recovery to baseline

Answer: C

Rationale: Laboratory based abnormalities of increased creatinine were observed in 98.3% of MONACH2 and 3 patients on abema. Reversible increases in SCr 15-40% over baseline. Overall, creatinine rises typically occurred after the first cycle, remained elevated but stable for treatment duration, and were reversible upon abeam discontinuation

Therapy for Non-Invasive Breast Cancer: Rachel L. Yung, MD

Question 1: A 45yo premenopausal woman with a biopsy with an incidental finding of classic LCIS. Her case was evaluated by surgery, radiology and pathology and pathology was concordant. The patient would like to consider risk reducing treatment. Appropriate treatment options include:

A) Anastrozole
B) Tamoxifen
C) Raloxifene
D) any of the above

Answer: B

Rationale: B is the answer because she is premenopausal.

Question 2: A 58yo healthy patient had a screen detected diagnosis of ER+ DCIS found after calcifications were found on screening mammogram. She underwent a lumpectomy without a sentinel lymph node biopsy which demonstrated a 5mm focus of invasive ductal carcinoma and 25mm of DCIS. The closest margin is 1mm of DCIS anteriorly. What further surgery does she need:

A) none
B) sentinel lymph node biopsy
C) re-excision to 2mm margin
D) sentinel lymph node biopsy and re-excision to 2mm

Answer: B.

Rationale: Given that this is DCIS with an invasive component it defers to Invasive treatment recommendations which states no tumor on ink as standard for margin and need for a SLNB for all invasive cancers.

Adjuvant Therapy for Breast Cancer : William R. Gwin III, MD

Question 1: A 33 year old woman with a BRCA1 mutation is found at lumpectomy to have a 2.5 cm high grade, ER negative and HER2 negative tumor. The sentinel node biopsy is negative. Which chemotherapy regimen is not appropriate?

A) Dose sense A/C followed by paclitaxel
B) Paclitaxel/Carbo + Pembrolizumab -> A/C + Pembrolizumab
C) Carboplatin and gemcitabine
D) T/C (Docetaxel and Cyclophosphamide)

Answer: C
Rationale: There are no randomized trials evaluating the role of regimen C in adjuvant breast cancer

Question 2: The patient above now wants to have a bilateral mastectomy because she was told that her survival from breast cancer in the next 5 years will be improved compared to the excision alone followed by radiation. You tell her that this information is:

A. True
B. False

Answer: B

Rationale: There is no survival benefit associated with bilateral mastectomies in unselected women with early stage breast cancer over that provided by lumpectomy and adjuvant radiation therapy. Also recently in JAMA, use of and Mortality After Bilateral Mastectomy Compared With Other Surgical Treatments for Breast Cancer in California, 1998-2011; For the small minority of patents with BRCA 1 or 2 germline mutations, prophylactic contralateral mastectomy is predicted to result in survival advantage over no surgery.

Question 3: A 45-year-old woman has a clinical stage III, HER2 amplified breast cancer with palpable lymph nodes. You offer her AC-THP or TCHP. Her EF is 67% and she has no history of HTN. You tell her that the risk of symptomatic congestive heart failure if she receives AC-THP is

A. 1-3%
B. 3-5%
C. 6-8%

Answer: A

Rationale: 15% with any clinically significant decrease in EF but only 1-3% are symptomatic.

Question 4: A 67 year old woman has a screening mammogram and is found to have breast calcifications. A biopsy is performed and demonstrates ER positive, PR positive, HER2 negative invasive adenocarcinoma. She undergoes lumpectomy and sentinel lymph node biopsy. The cancer measures 1.5cm and two of four sentinel nodes are positive one of which is a macrometastasis. She is anticipated to undergo radiation therapy to complete breast conservation intent. If an axillary lymph node dissection is performed which is expected?

A) Decrease in locoregional recurrence and improved overall survival.
B) Decrease in locoregional recurrence and improved disease free survival.
C) No change in locoregional recurrence and an improved overall survival.
D) No improvement in disease free survival or overall survival.

Answer: D

Rationale: The American College of Surgeons Oncology Group (ACOSOG) study Z0011 trial was designed to address the need for completion ALND for patients with T1 or T2 tumors that were clinically node negative and had less than three positive sentinel nodes; all patients were treated with radiation to the breast. With a median follow-up of over 6 years there was no significant difference in survival (DFS and OS) or locoregional control. Reference: JAMA. 2013 Oct 9;310(14):1455-61

Metastatic Breast Cancer : Sara A. Hurvitz, MD, FACP

Question 1: A 56yo woman presented to her local ER with RUQ pain and left hip pain. Her last medical examination was more than 20 years ago after the birth of her son. Exam was notable for mild scleral icterus, a large right breast mass with overlying skin discoloration and ulceration, palpable right axillary adenopathy and a tender, distended abdomen with hepatomegaly. Laboratory data was most significant for mild Grade 1 hyperbilirubinemia. CT CAP revealed lesions suspicious for metastases involving adenopathy, bilateral lungs, liver and bones. A biopsy of the breast mass and liver confirm invasive ductal carcinoma, ER 0% PR 0% HER2 3+.

A. Docetaxel and Trastuzumab
B. Tucatinib, capecitabine and trastuzumab
C. Ado-trastuzumab emtansine
D. Taxane (docetaxel q3 weekly or paclitaxel weekly) trastuzumab and pertuzumab

Answer: D

Rationale: Choice D is optimal based on the CLEOPATRA trial (Swain et al Lancet Oncol) which established docetaxel, trastuzumab and pertuzumab as the first line treatment of choice for a patient with HER2+ MBC based upon significant improvement in PFS and OS when compared to docetaxel and trastuzumab. NCCN guidelines include weekly paclitaxel with trastuzumab and pertuzumab as an option, based on tolerability and efficacy noted in a phase II trial.

Question 2: Eight years ago, a 66yo woman was diagnosed with a Stage 1 ER+ HER2 1+, FISH- breast cancer with a low risk 21-gene recurrence score. She underwent breast conservation surgery, radiation therapy and went on to complete 5 years of adjuvant anastrozole. Two years after stopping anastrozole, she presented to her internist reporting worsening back pain. Imaging revealed diffuse osseous lesions suspicious for metastases. Biopsy of a bone lesion confirmed recurrent ER+ HER2- metastatic breast cancer. Which of the following is the preferred first-line treatment choice?

A. Capecitabine
B. T-DXd (trastuzumab deruxtecan)
C. Endocrine therapy plus a CDK4/6 inhibitor
D. Inavolisib plus palbociclib plus fulvestrant
E. Elacestrant

Answer: C

Rationale: The addition of a CDK4/6 inhibitor to endocine therapy (aromatase inhibitor or fulvestrant) has been shown to improve the progression free survival and in some trials (with ribociclib), the overall survival for first-line treatment of HR+ metastatic breast cancer. The FDA approved the use of three CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib, respectively) in the 1st line treatment of ER+ metastatic breast cancer based upon the PALOMA2, MONALEESA-2, MONALEESA-3, MONALEESA-7 and MONARCH-3 trials. The RIGHT CHOICE trial demonstrated superiority of a CDK4/6i (ribociclib) plus endocrine therapy compared with multiagent chemotherapy for high risk symptomatic HR+ metastatic breast cancer in the first line setting, making capecitabine the wrong choice. While T-DXd is approved for HER2-low and HER2-ultralow breast cancer based on the findings of DESTINY-Breast04 and DESTINY-Breast06, it should be used after a CDK4/6i-based/endocrine therapy. The use of inavolisib plus palbociclib and fulvestrant is indicated for patients with relapsed PIK3CA-mutated breast cancer within 12 mos of adjuvant endocrine therapy.

Wednesday, October 8

Gynecologic Oncology - Ovarian Cancer : Kalyan Banda, MD

Question 1: A 36-year-old woman presents to her gynecologist. Her sister was recently diagnosed with ovarian cancer, and she is concerned about her risk of developing this disease. The patient's sister underwent genetic counseling and tested negative for any known germline conditions associated with ovarian cancer. The patient had menarche at the age of 10. She is married and works as a social worker. She has taken oral contraceptive pills for the past 9 years and is G0P0. She exercises three times a week, and her BMI is 32. She follows a vegetarian diet.

Which of the following factors is associated with a decreased risk of developing ovarian cancer?

A) BMI of 32
B) Prior oral contraceptive use
C) Early menarche
D) Nulliparity

Answer: B

Question 2: A 62-year-old G0P0 post-menopausal woman presents to her primary care physician with complaints of bloating and urinary frequency over the past 2 months. On examination, she is found to have a pelvic mass, and pelvic ultrasound shows a 6-cm mass in the left adnexa and trace fluid in the cul-de-sac. CT scan confirms the presence of a pelvic mass involving the left adnexa, demonstrates an atrophic right adnexa, and does not show other enlarged lymph nodes or intra-abdominal metastases. She is referred to her gynecologist, who performs a hysterectomy and left salpingo-oophorectomy. Pathology reveals a 7-cm, grade 3 endometrioid carcinoma involving the left ovary in a background of endometriosis. The endometrium is atrophic, a small fibroid is present, and the left fallopian tube is unaffected. She is referred for further management.

What do you recommend?

A) Observation
B) Three cycles of chemotherapy with carboplatin and paclitaxel
C) Six cycles of chemotherapy with carboplatin and paclitaxel
D) Exploratory laparotomy, omentectomy, right salpingo-oophorectomy, lymphadenectomy, and peritoneal biopsies

Answer: D

Question 3: A 66-year-old woman presented with right lower quadrant pain and general abdominal discomfort. The patient underwent CT of the abdomen and pelvis with contrast, which showed a large cystic mass about the central pelvis extending slightly to the left, measuring 10.7 x 12.0 x 11-cm in size. A smaller cystic lesion in the right adnexa measuring 5.6 x 3.6-cm. The patient underwent staging laparotomy with bilateral salpingo-oophorectomy, pelvic washings, omentectomy, sigmoid colectomy with colostomy placement, and appendectomy. She underwent optimal cytoreduction. Postsurgical pathology was positive for high-grade serous ovarian cancer of the left ovary with adjacent organ involvement into the right ovary, omentum, urinary bladder, and sigmoid colon with peritoneal ascitic fluid positive for malignancy. The patient is negative for somatic or germline BRCA 1 and BRCA2 mutations. She is homozygous recombinant deficiency negative. The patient does not carry a BRCA1 or BRCA2 mutation, and her tumor is negative for these mutations and homologous recombination deficiency. The patient had a complete response following six cycles of carboplatin, paclitaxel, and bevacizumab.

Which of the following is the most appropriate regimen for the management of this patient?

A) Maintenance bevacizumab
B) Maintenance bevacizumab and Olaparib
C) Maintenance bevacizumab and niraparib
D) Maintenance olaparib

Answer: A

Question 4: A 66-year-old woman presented with right lower quadrant pain and general abdominal discomfort. The patient underwent CT of the abdomen and pelvis with contrast, which showed a large cystic mass about the central pelvis extending slightly to the left, measuring 10.7 x 12.0 x 11-cm in size. A smaller cystic lesion in the right adnexa measuring 5.6 x 3.6-cm. The patient underwent staging laparotomy with bilateral salpingo-oophorectomy, pelvic washings, omentectomy, sigmoid colectomy with colostomy placement, and appendectomy. She underwent optimal cytoreduction. Postsurgical pathology was positive for high-grade serous ovarian cancer of the left ovary with adjacent organ involvement into the right ovary, omentum, urinary bladder, and sigmoid colon with peritoneal ascitic fluid positive for malignancy. The patient is negative for somatic or germline BRCA 1 and BRCA2 mutations. She is homozygous recombinant deficiency. The patient does carry a BRCA1 or BRCA2 mutation, and her tumor is positive for these mutations and homologous recombination deficiency. The patient had a complete response following six cycles of carboplatin, paclitaxel, and bevacizumab.

Which of the following is the most appropriate regimen for the management of this patient?

A) Maintenance bevacizumab
B) Maintenance bevacizumab and Olaparib
C) Maintenance bevacizumab and niraparib
D) Maintenance olaparib

Answer: B

Question 5: A 43-year-old woman is diagnosed with Stage IIIC recurrent ovarian cancer. She undergoes a complete gross resection of disease and treatment with 6 cycles of carboplatin and paclitaxel chemotherapy. She is BRCA wild-type. CT chest, abdomen, and pelvis scan at the end of treatment show she is in remission. Three months later, she is found to have recurrent disease.

Which of the following is the most appropriate treatment at this time?

A) Bevacizumab in combination with carboplatin and gemcitabine
B) Cediranib in combination with carboplatin and paclitaxel
C) Bevacizumab in combination with liposomal doxorubicin
D) Bevacizumab in combination with gemcitabine

Answer: C

Gynecologic Oncology - Cervical and Endometrial Cancers : BJ Rimel, MD

Question 1: Which of the following factors are incorporated into the updated FIGO 2023 staging for endometrial cancer?

A) Histologic subtype
B) Histologic grade
C) Extent of LVSI
D) Anatomic extent of disease
E) All of the above

Answer: E) All of the above

Rationale: This is the "new" staging system for endometrial cancer. It adds the histology and LVSI to the criteria and does not reflect any of the current clinical trials.

Question 2: You are meeting a new patient with stage IIIC2 grade 3 endometrioid endometrial cancer. On imaging, there is residual paraaortic lymphadenopathy. Pathologic and molecular assessment reveals a tumor with MSI, p53 wild-type, Her-2neu 1+ on IHC, no POLE mutation. What treatment would you recommend for her?

A) Carboplatin, paclitaxel, dostarlimab followed by dostarlimab maintenance
B) Carboplatin, paclitaxel, pembrolizumab followed by pembrolizumab maintenance
C) Carboplatin, paclitaxel, trastuzumab followed by trastuzumab maintenance
D) Carboplatin and paclitaxel
E) A or B

Answer: E) A or B

Rationale: FDA Approvals – primary advanced or recurrent endometrial carcinoma

Aug 1, 2024: Dostarlimab-gxly with carboplatin & paclitaxel followed by dostarlimab maintenance (expanded from initial indication for only patients with dMMR/MSI-H tumors)

June 17, 2024: Pembrolizumab with carboplatin & paclitaxel followed by pembrolizaumb maintenance.

CNS Cancers : Vyshak Venur, MD

Question 1: A 44-year gentleman had a first-time generalized seizure while at work. He was taken to the local emergency room and as a part of his work up he had a CT head which showed a lesion in the right frontal lobe. A brain MRI w/wo contrast was obtained which confirmed a 2x2 cm lesion in the right frontal lobe, with T2 FLAIR hyperintensity and no-contrast enhancement. He was started on dexamethasone and levetiracetam and taken to the operative. A gross total resection was performed.

Which of the following molecular features in the tumor would provide the best survival advantage?

A) MGMT methylation
B) IDH mutation
C) Chromosome 10p loss
D) TERT promoter mutation
E) EGFRvIII mutation

Answer: B

Rationale: IDH mutation. Point mutation in the IDH gene (R132H being the most common) provides significant survival advantage for patients with high grade glial neoplasm.

Question 2: A 68-year-old male was diagnosed with left parieto-temporal glioblastoma, WHO grade 4, IDH wild type, MGMT methylated, when he presented with progressive reading and language difficulty. After complete resection of the tumor the patient received standard six -week course of radiation and temozolomide. His symptoms improved with occupational and speech therapy. His first MRI brain 4 weeks after completion of chemoradiation showed no new lesions. He was then started on maintenance temozolomide. He presents for follow up today, has no new symptoms but MRI brain shows new contrast enhancing lesion in the superior and anterior margin of the surgical cavity with surrounding T2/FLAIR hyperintensity.

What is the best next step?

A) Since the patient has a new lesion on temozolomide, stop temozolomide and send the patient to hospice

B) Given the new lesion within three months of concurrent chemoradiation, radiosurgery should be considered

C) Since the new lesion is contrast enhancing on brain MRI, switch to bevacizumab

D) The patient will likely benefit with continuation of temozolomide and short interval follow up MRI brain

Answer: D

Rationale: The patient will likely benefit with continuation of temozolomide and short interval follow up MRI brain. In the first 12 weeks after completion of radiation therapy MRI brain could show features concerning for disease progression but might be transient and reflect pseudoprogression.

Question 3: A 27-year-old woman was noted to have a right temporal lobe lesion when he sustained a new onset focal seizure. She underwent gross total resection of the tumor and the pathology was consistent with oligodendroglioma, WHO grade 2. The tumor was positive for 1p/19q co-deletion and IDH R132H mutation by sequencing. Following the surgery, she was treated with radiation therapy and six cycles of procarbazine, lomustine and vincristine. She tolerated the treatment well and is currently on surveillance.

Responses:

A) 1-2 years
B) 4-5 years
C) 8-10 years
D) 12-15 years

Answer: D

Rationale: Historically, the patient with anaplastic oligodendroglioma were treated with radiation therapy alone after surgery. The RTOG 9402 study evaluated the role of chemotherapy in addition to radiation therapy in patients with anaplastic oligodendroglioma and anaplastic oligoastrocytoma (which are now classified as anaplastic astrocytoma). Among patients with anaplastic oligodendroglioma, carrying the pathognomonic 1p/19q co-deletion the median overall survival was 14.7 years with RT plus procarbazine, lomustine, and vincristine compared to 7.3 years with RT alone. The EORTC 26951 also showed the median overall survival was not reached for patients treated with RT plus PCV at 140 months, while patients treated with RT alone had a median survival of 112 months.

Reference: 1. RTOG 9402: J Clin Oncol. 2013 Jan 20; 31(3): 337-343

Integrative Medicine : Shannon Fogh, MD

Question 1: What is the order of "the most evidence" to the "least evidence" supporting the use of integrative therapies with oncology patients:

A. Dietary/botanical supplements, mind-body therapies, acupuncture
B. Mind-body therapies, acupuncture, dietary/botanical supplements
C. Acupuncture, dietary/botanical supplements, mind-body therapies

Answer: B

Rationale: The strongest body of evidence supports the use of mind-body therapies for anxiety/stress, depression/mood, quality of life, fatigue, and sleep; acupuncture for pain management and CIPN; and there is very limited evidence in general on the use of dietary/botanical supplements.

Question 2: ASCO has published and endorsed evidence-based guidelines on the use of specific integrative therapies during oncology care.

A. True
B. False

Answer: A

Rationale: ASCO endorsed the Society for Integrative Oncology's 2017 Clinical Practice Guidelines on the Use of Integrative Therapies During and After Breast Cancer Treatment and published the joint SIO-ASCO 2022 guideline on Integrative Medicine for Pain Management in Oncology and the SIO-ASCO 2023 guideline on Integrative Oncology Care of Symptoms of Anxiety and Depression in Adults with Cancer. In addition, both ASCO and NCCN have included has included some integrative therapies in symptom management guidelines related to pain, anxiety/depression, and CINV.

Question 3: According to the 2022 Society for Integrative Oncology – ASCO integrative medicine for pain management in oncology guidelines, acupuncture has a moderate recommendation based on an intermediate level of evidence for what kinds of pain? Select all that apply.

A. Aromatase Inhibitor-Related Joint Pain
B. General Cancer Pain or Musculoskeletal Pain
C. Procedural or Surgical Pain
D. Pain during palliative care

Answer: A and B

Supportive Care: Keith D. Eaton, MD, PhD

Question 1: Which of the following treatments should be recommended for the prevention of chemotherapy induced peripheral neuropathy?

A) Acetyl-L-carnitine
B) Calcium/Magnesium
C) Vitamin E
D) Pyridoxine (B6)
E) None of the above

Answer: E

Rationale: Although several treatments have been proposed for the prevention of chemotherapy induced peripheral neuropathy, none has been validated in prospective randomized clinical trials and none should be recommended.

Question 2: Which of the following factors is predictive of increased likelihood of experiencing chemotherapy related nausea and vomiting?

A) Male gender
B) Younger age
C) History of heavy alcohol use
D) Good performance status E. Use of antidepressants

Answer: B

Rationale: The following factors increase the likelihood of CINV: younger age, female gender, history of prior emesis with chemotherapy, anxiety, history of motion sickness, history of morning sickness with prior pregnancy. The likelihood of CINV is decreased in patients who have a prior history of alcohol abuse. Fractionated regimens are better tolerated than unfractionated regimens. --- Which of the following agents has no demonstrated benefits in randomized clinical trials for cancer cachexia? A. Olanzapine B. Dexamethasone C. Megestrol D. Dronabinol E. none of the above, all agents have demonstrated benefit in RCTs. Answer D. There have been limited clinical trials in cancer cachexia for all the agents above. There are trials demonstrating at least limited benefit for all agents except dronabinol. Olanzapine is emerging as a preferred option based on magnitude of benefit and side effect profile. Megestrol and dexamethasone both have a modest effect in weight gain but have significant side effects.

Radiation Oncology - Multi-Disciplinary [Breast, Lung, Colorectal, and Palliative] : Lisa Ni, MD

Question 1: By what mechanism does radiation therapy treat malignancy?

A) Direct cytotoxicity via DNA damage
B) Disruption of tumor vasculature
C) Impairing cell membrane integrity and denaturing proteins
D) Release of neo-antigens facilitating immune recognition
E) All of the above

Answer: E

Rationale: The primary mechanism by which radiation therapy treats malignancy is direct cytotoxicity via DNA damage—ionizing radiation induces DNA double-strand breaks that are difficult for cancer cells to repair, leading to cell death. However, radiation also disrupts tumor vasculature, impairs cell membrane integrity, denatures proteins, and crucially, releases neo-antigens that facilitate immune recognition and anti-tumor immune responses. Thus, the correct answer is E) All of the above, as all listed mechanisms contribute to the therapeutic effect.

Question 2: What characteristic of a cell indicates its sensitivity to radiation damage, and for cancers determines the theoretical optimal fractionation?

A) Oxygen enhancement ratio
B) The alpha/Beta ratio
C) Dose-depth profile
D) The Bragg peak
E) Nucleus:cytoplasm ratio

Answer: B

Rationale: The alpha/beta ratio is a radiobiological parameter that reflects a cell or tissue's sensitivity to fractionation and radiation damage, guiding optimal dose/fractionation schedules for specific tumors. For example, tumors with a low alpha/beta ratio, such as prostate cancer, are more sensitive to larger fraction sizes.

Question 3: Why might a shorter radiation therapy treatment course be more beneficial than a longer one?

A) Patient convenience
B) Better local control based on tumor's alpha/Beta ratio
C) Widening the therapeutic window
D) Reduced cost
E) All of the above

Answer: E

Rationale: A shorter radiation therapy course can be more beneficial due to patient convenience, better local control based on the tumor's alpha/beta ratio, widening the therapeutic window, and reduced cost. Many modern hypofractionation regimens are supported by randomized trials and guidelines, showing non-inferior efficacy and safety, with improved logistics and cost-effectiveness.

Question 4: What is the most common particle used in radiation therapy?

A) Electrons
B) Protons
C) Photons
D) Neutrons
E) Carbon ions

Answer: C

Rationale: The most common particle used in clinical radiation therapy is photons (X-rays), which are employed in conventional external beam radiotherapy. While electrons, protons, and heavier ions are used in specific contexts, photons remain the standard due to their availability and established efficacy.

B-NHL, Indolent Non-Hodgkin Lymphoma : Solomon A. Graf, MD

Question 1: An 85 yo woman has a 14-year history of follicular lymphoma previously treated with rituximab-cyclophosphamide-vincristine-prednisone, then bendamustine-obinutuzumab, and most recently lenalidomide-rituximab. She has disease progression in multiple regions and increasing fatigue. LDH is wnl, repeat biopsy shows classic FL, and molecular testing of the biopsy reveals mutation of EZH2. Her PMH is significant for DM2 and HTN; ECOG PS = 2. She prioritizes convenience and low toxicity in treatment.

Of the following options, you recommend:

A) Mosunetuzumab, citing superior outcomes to alternatives in multiply R/R FL
B) Tisagenlecleucel, noting theoretical potential for cure
C) Tazemetostat
D) Radiation to symptomatic sites and hospice referral, explaining that any systemic treatments would likely be prohibitively toxic

Answer: C

Rationale: This question considers options for treating multiply relapsed FL. Tazemetostat is a first-in-kind inhibitor of Zeste Homolog 2 (EZH2). Gain of function EZH2 mutation is found in about 20-25% of FL and results in epigenetic silencing and B-cell proliferation. Importantly, EZH2 is biologically active in WT and mutant states, and tazemetostat can be effective in each case (though likely is more active in cases of EZH2 mutation). Mosunetuzumab is a bispecific T-cell engager administered intravenously that is associated with risk of low-grade CRS and cytopenias and has been tested chiefly in patients with ECOG PS 0-1. CD19 targeting CAR-T products have shown durable responses in multiply relapsed FL but are associated with significant toxicity and logistical challenges. While radiotherapy and hospice referral may be appropriate if preferred by the patient, tazemetostat is a low-risk, oral treatment option well suited for this case.

Question 2: A 24 yo man without significant medical history and who feels well has an incisional biopsy of a > 5 cm cervical LN. This shows architectural effacement by a follicular pattern of monotonous appearing B-lymphocytes that mark positive for CD10, BCL6, and CD20 on IHC and show no t(14;18) on FISH. PET/CT and bone marrow studies show FDG avid cervical adenopathy and no evidence of advanced stage disease. You expect additional pathologic analysis to show:

A) Presence of t(11;18)
B) Strong BCL2 expression
C) TP53 mutation
D) Ki67 > 30% in malignant cells

Answer: D

Rationale: This question stem describes pediatric-type follicular lymphoma (PTFL), an uncommon subtype of FL recognized in both WHO and ICC classification schemes. It typically presents in younger, male patients and involves limited nodes in the head and neck or inguinal regions. The pathology is distinct from classic FL for being negative for t(14;18) and BCL2 expression with a relatively high proliferation index (i.e., Ki-67 > 30%). t(11;18) can be found in gastric EMZL, can predict lack of response to H. pylori therapy, and is without known relevance to PTFL. TP53 mutation is not associated with PTFL, which has a low genomic complexity. Treatment of PTFL in adults prioritizes local therapy for stage I or II disease with excision or radiotherapy.

B-NHL, Aggressive - Mengyang Di, MD, PhD

Question 1: A 71-year-old woman is treated with Pola-RCH_P for DLBCL, but experiences relapse 18 months later. Which of the following is the most appropriate treatment option?

A) Oral Selinexor
B) Pirtobrutinib if non-GCB subtype
C) Lisocabtagene maraleucel
D) Allogeneic transplantation after RBAC chemotherapy

Answer: C

Rationale: The PILOT trial tested lisocabtagene maraleucel, a CD19-directed chimeric antigen receptor (CAR) T-cell product, as second-line treatment in adults with relapsed or refractory large B-cell lymphoma not intended for HSCT, including patients older than 70. This study showed an 80% overall response rate to therapy, with no treatment-related deaths, and led to FDA approval of this CAR_T cell in this setting.

Question 2: A 68-year-old man was treated with RCHOP for DLBCL in 2018. He had relapse 2.5 years after completing frontline treatment. He received salvage chemotherapy R-GemOx, achieved complete remission after salvage chemo, and received autologous stem cell transplant for consolidation. He unfortunately had relapse again 3 years after transplant. Glofitamab was being discussed as the next therapy. What is the mechanism of action for glofitamab?

A) CD19*CD3 bispecific T cell engager
B) CD20*CD3 bispecific T cell engager
C) CD19 antibody
D) Antibody conjugate drug

Answer: B

Rationale: Glofitamab is a CD20*CD3 bispecific T cell engager. It is approved by the FDA in 2024 to treat large B cell lymphoma in the 3rd line setting and beyond. It is an iv infusion, given for fixed duration (12 cycles, 21 days per cycle). The common side effects include cytokine release syndrome, infection, cytopenia. Step-up dosing, Obinutuzumab pre-therapy, steroids during the first two cycles, inpatient administration for the first dose are strategies to mitigate CRS.

Question 3: A 67-year-old man was diagnosed with MCL at age 62 but had no significant comorbidities. As frontline therapy, he received BR for 6 cycles followed by rituximab maintenance for 2 years. He experienced relapse at age 63 with diffuse lymphadenopathy. At that time, he was treated with ibrutinib (560 mg) for 2 years. Now, he has a diffuse relapse with pancytopenia, and bone marrow–positive disease with extensive lymphadenopathy.

In your current practice, what would you recommend as the optimal next-line treatment for this 67-year-old patient?

A. Acalabrutinib
B. Brexucabtagene autoleucel (brexu-cel)
C. Lenalidomide plus rituximab
D. Mosenutuzumab plus polatuzumab vedotin

Answer: B.

Rationale: Based on the results of the ZUMA-2 trial, brexu-cel received FDA approval for the treatment of adult patients with R/R MCL. Brexu-cel elicits high ORR (87%) and long OS (46.6 months). Acalabrutinib, a covalent BTK inhibitor, may not be effective in the case of progression on ibrutinib and covalent BTK inhibitor resistance. Lenalidomide plus rituximab is a less aggressive regimen. Mosenutuzumab plus polatuzumab vedotin is currently not approved by the FDA in MCL.

T-Cell Lymphoma - NHL : Michael Khodadoust, MD, PhD

Question 1: A 57-year old male was presented with night sweats and palpable lymphadenopathy and was diagnosed with ALK negative anaplastic large cell lymphoma. What is the best treatment approach?

A) CHOEP
B) CHOP
C) R-CHOP
D) Brentuximab-CHP

Answer: D

Rationale: Brentuximab-CHP was associated with both an improved progression-free survival and overall survival as compared to CHOP in the randomized phase 3 ECHELON-2 trial for both ALK positive and ALK negative anaplastic large cell lymphoma.

Question 2: Which is a black box warning for brentuximab?

A) Interstitial lung disease
B) Progressive multifocal leukoencephalopathy (PML)
C) Peripheral neuropathy
D) Nephrotic syndrome

Answer: B

Rationale: The findings of a CD4+ T-cell lymphoma with CCR4 expression in a patient of Japanese descent with hypercalcemia raises the possibility of a diagnosis of Adult T-cell leukemia/lymphoma (ATLL). Testing for the HTLV-1 virus is essential to help confirm the diagnosis and exclude other possible diagnoses such as Sezary syndrome or PTCL-NOS. EBV testing is important in establishing the diagnosis of NKT lymphoma, however the lack of CD56 expression and the clinical presentation makes this diagnosis less likely. A histone deacetylase inhibitor may be appropriate therapy for Sezary syndrome but would not be the best initial therapy for ATLL. Immunotherapy such as nivolumab has been associated with hyperprogression in ATLL and therefore would not be an appropriate treatment choice.

Hodgkin Lymphoma : Ryan C. Lynch, MD

Question 1: A 21 year old female with new diagnosis of stage IA classical Hodgkin lymphoma completes 2 cycles of ABVD and 20 Gy of consolidative radiotherapy to the mediastinum. She has achieved a complete metabolic response (Deauville 2).
Which of the following would be most appropriate to recommend for follow up?

A) Surveillance CT scans every 6 months for the first 5 years.
B) Post-radiation biopsy to confirm remission
C) Regular mammograms and/or breast MRI starting 7 years after radiation
D) Surveillance PET/CT at one year post treatment

Answer: C

Rationale: Female patients who have breast tissue radiated as part of treatment are at higher risk of breast cancer and should have earlier surveillance. Patients with a complete metabolic response do not require post treatment biopsies, but in patients with persistent or new FDG uptake, a biopsy should be considered. Surveillance imaging is at clinician discretion taking into account age, stage, and risk of relapse. Surveillance imaging in the absence of clinical findings/symptoms should be discontinued at 2 years. PET/CT should NOT be routinely performed in remission, but may be performed for suspected relapse.

Question 2: A 62 year old female has been diagnosed with Stage IVA classical Hodgkin lymphoma with extensive lymphadenopathy above and below the diaphragm as well a lung involvement with bilateral pleural effusions. This patient cannot walk more than 20 feet without needing to rest due to shortness of breath. Pre-treatment echocardiogram is within normal limits.

Based on this discussion, what is the most reasonable chemotherapy regimen to recommend?

A) Nivolumab + AVD
B) Brentuximab+AVD
C) ABVD
D) Pembrolizumab

Answer: A

Rationale: Brentuximab vedotin + AVD is associated with superior PFS and OS compared to ABVD in advanced stage Hodgkin lymphoma, with the majority of benefit seen in high risk patients (IPS 4-7, stage IV). In addition, nivolumab+AVD is associated with superior PFS compared to brentuximab vedotin+AVD in advanced stage Hodgkin lymphoma. Pembrolizumab monotherapy is not approved or indicated for untreated patients with classical Hodgkin lymphoma

Question 3: A 30 year old female have presented with 6 months of intermittent fevers, drenching night sweats, dry cough, and loss of 15% of body weight. CT scan demonstrate widespread lymph adenopathy above and below the diaphragm as well as splenomegaly with multiple 2-3 cm splenic nodules. An excisional biopsy of a right axillary lymph node demonstrated lymphocyte pre-dominant Hodgkin lymphoma.

What would be the most reasonable upfront treatment regimen?

A) Observation
B) ABVD
C) escalated BEACOPP
D) R-CHOP

Answer: D

Rationale: This is a symptomatic patient with lymphocyte predominant Hodgkin lymphoma, so observation is not indicated in this case. This subtype of Hodgkin lymphoma is CD20-positive, so patients who receive chemotherapy should also receive rituximab. R-CHOP is one effective regimen in this setting, but R-ABVD has also been studied. R-CHOP can be considered for patients at high risk of occult transformation as these patients transform for diffuse large B-cell lymphoma.

Thursday, October 9

Infectious Disease Complications : Denise McCulloch, MD, MPH

Question 1: All cancer patients and hematopoietic cell transplantation recipients with febrile neutropenia require empiric vancomycin?

Answer: False

Rationale: Most experts agree that empiric vancomycin should be reserved for specific patients including those with signs of clinically apparent serious catheter related infection, skin or soft tissue infection or hemodynamic instability. Furthermore, multiple studies have shown increased rates of vancomycin for inappropriate indications and/or durations.

Question 2: Which of the following medications is first-line therapy for invasive aspergillosis?

A. Voriconazole
B. Posaconazole
C. Micafungin
D. Fluconazole
E. A and B
F. C and D

Answer: E

Rationale: Randomized controlled trial data have shown that posaconazole is non-inferior to voriconazole for primary treatment of invasive aspergillosis with respect to all-cause mortality and adverse events.

Question 3: All of the following are risk factors for CMV reactivation after HCT except:

A. Haploidentical transplant
B. GVHD
C. CD4 count >200
D. Cord transplant
E. Treatment with steroids

Answer: C

Rationale: Risk factors for CMV reactivation after HCT include T-cell dysfunction or deficiency and lymphopenia, including low CD4 counts. Furthermore, certain types of allogenic transplant are at higher risk, including cord transplantation, haplo, HLA-mismatched, and T-cell depleted. Finally, GVHD and treatment with high-dose steroids are important risk factors for CMV reactivation.

Familial Syndromes : Andrew B Stergachis, MD, PhD

Question 1: What accounts for different types of cancer occurring in different members of the same family with Lynch syndrome?

A) Different germline mutation
B) Random tissue distribution of the second hit
C) Random tissue distribution of secondary mutations
D) Modifier genes inherited from the unaffected parent
E) Both B & C

Answer: E

Rationale: Lynch syndrome is a genetically heterogenous disorders of DNA mismatch repair deficiency, transmitted as an autosomal dominant trait, but that follows Knudson's "two-hit" hypothesis for tumor suppressor genes. Heterozygosity for DNA mismatch repair by itself is probably insufficient to lead to increased mutations. Once a "second hit" occurs, however, in the wild type (non-mutated) allele inherited from the unaffected parent, then mutations accumulate in other genes, including other tumor suppressor genes, as well as proto-oncogenes. Both of these processes occur randomly and dictate the tissue distribution of resulting tumors.

Question 2: Based on the information below alone, which of these individuals is least likely to benefit from additional germline genetic testing for a possible hereditary cancer syndrome?

A) An individual with a pathogenic TP53 variant detected in blood with a variant allele fraction (VAF) of 30%.
B) An individual with a family history of exocrine pancreatic cancer in her mother.
C) An individual with a single melanoma prior to age 30.
D) An individual with an adrenocortical carcinoma (ACC).
E) An individual with prostate cancer and a family history of Ashkenazi Jewish ancestry.

Answer: C

Rationale: Somatic TP53 variants detected in blood could arise from either clonal hematopoiesis or constitutional post-zygotic mosaicism. Testing of cultured skin fibroblasts, tumor, and/or other alternative tissues is recommended to aid in diagnostic clarity when such a variant is identified. Individuals who have a mosaic TP53 variant identified outside of the hematopoietic lineage are managed per usual Li Fraumini Syndrome (LFS) management recommendations, whereas individuals with a mosaic TP53 variant limited to hematopoietic cells are not. Note that saliva contains hematopoietic cells, so saliva-based testing should not be used to augment blood-based testing when making this determination.

Pancreatic cancer can be seen in association with several hereditary cancer syndromes, and current NCCN guidelines state that genetic testing is clinically indicated in individuals who themselves do not have cancer, but have a family history of pancreatic cancer in a first degree relative.

Adrenocortical carcinoma (ACC), particularly when occurring during childhood, is most commonly associated with Li-Fraumeni syndrome, where it can account for 50-80% of childhood cases of ACC. According to current NCCN guidelines, which are partially based upon the Chompert criteria, genetic testing is clinically indicated in individuals with ACC present at any age.

There are three “founder” mutations responsible for hereditary breast ovarian cancer syndrome prevalent in the Ashkenazi Jewish population (BRCA1 185delAG, BRCA1 5382insC, BRCA2 6174delT). In addition to breast cancer, these founder mutations also increase the risk for prostate cancer, and current NCCN guidelines state that genetic testing is clinically indicated in individuals with prostate cancer who have Ashkenazi Jewish ancestry.

Although there are several hereditary cancer syndromes that can increase the risk of melanoma. Most individuals with melanoma do not have an identifiable hereditary predisposition and as such current guidelines do not recommend routine genetic testing for individuals with a single melanoma..

Hematology Pharmacology Pearls : Zak Cerminara, PharmD, BCOP

Question 1: AB, a 58-year-old man, presents with increasing feelings of fatigue and back pain.

PMH:

- Heart failure with reduced ejection fraction
- Diabetes
- Hyperlipidemia

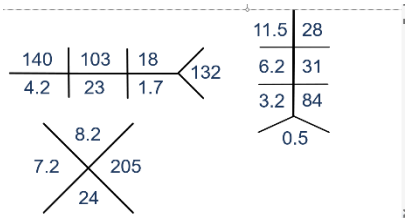
Vitals:

- Weight: 96 kg
- Blood pressure: 124/76

Current medications:

- Metformin 1000 mg PO BID
- Metoprolol 50 mg PO daily
- Lisinopril 20 mg PO daily
- Atorvastatin 20 mg PO daily
- Gabapentin 300 mg PO BID

Furosemide 20 mg PO daily PRN weight gain



Labs:

- MSpike 9.7 g/dL
- Kappa free light chains (KFLC): 746.9 mg/dL
- Lambda free light chains (LFLC): 0.6 mg/dL
- Free light chain ratio (FLCR): 1244
- Beta 2 Micro (B2M): 7.1 µg/mL
- IgG: 10,385 mg/dL IgA: 14 mg/dL IgM: 23 mg/dL

Imaging:

- MRI
  - Spine: Diffuse lumbar spine marrow replacing process compatible with infiltrative disorder such as multiple myeloma. At the L1 vertebral body level, there is enhancing epidural tumor, greater to the left of midline results in mild to moderate AP spinal canal stenosis without compression of the conus medullaris
  - Pelvis: diffuse malignant process. No evidence of fracture

Procedures:

- Bone marrow biopsy:
  - Abnormal plasma cell population 24% by flow cytometry.
  - >60% plasma cells by CD138 immunohistochemistry.
  - FISH with t(11;14)
  - Cytogenetics abnormal with loss of Y chromosome in 7 of 20 cells.

AB is diagnosed with standard risk IgG Kappa multiple myeloma. What would you recommend as first line therapy for AB?

A) Bortezomib, lenalidomide, dexamethasone (VRd)
B) Carfilzomib, lenalidomide, dexamethasone (KRd)
C) Daratumumab, lenalidomide, dexamethasone (DRd)
D) Bortezomib, lenalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide (VRD-PACE)
E) Daratumumab, bortezomib, melphalan, prednisone

Answer: A

Question 2: Based on the initial treatment you selected, what ancillary medications would AB require in addition to the chemotherapy? (Choose all that apply)

A) Aspirin 81 mg PO daily
B) Apixaban 5 mg PO BID
C) Sulfamethoxazole/trimethoprim 800/160 mg PO daily MWF
D) Acyclovir 400 mg PO BID
E) Aprepitant 130 mg IV on days of chemotherapy
F) Posaconazole 300 mg PO daily

Answer: A&D

Rationale: Because we chose VRd, which contains an immunomodulator (IMiD; lenalidomide) and a proteasome inhibitor (PI; bortezomib) we need to ensure the patient has:
VTE prophylaxis due to the combination of IMiD and high dose dexamethasone. Depending on the patient's VTE risk, anything from aspirin 81 mg daily to full anticoagulation is appropriate.
Nothing about this patient suggest he is at higher-than-average risk for VTE currently, so low dose aspirin therapy is appropriate.
HSV/VZV prophylaxis due to PI.
Alternatives: valacyclovir 500 mg PO BID, famciclovir 250 mg PO BID
Note: these drugs will likely need dose reduction for renal impairment, which is common in myeloma

Question 3: AB has undergone 6 cycles of VRd with his oncologist. He has had worsening neuropathy leading to delays in treatment. He has also developed atrial fibrillation (AFib). His myeloma markers have all plateaued.
Current medications:

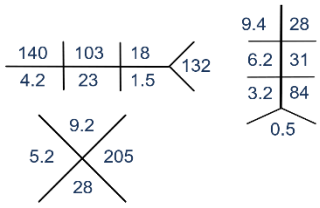
- Acyclovir 400 mg PO BID
- Apixaban 5 mg PO BID
- Metformin 1000 mg PO BID
- Metoprolol 50 mg PO BID
- Lisinopril 40 mg PO daily
- Atorvastatin 20 mg PO daily
- Gabapentin 600 mg PO TID
- Oxycodone 5 mg PO Q6H PRN pain

Furosemide 20 mg PO daily PRN weight gain

Vitals:

- Weight: 89 kg
- Blood pressure: 142/96

Labs:



- MSpike 2.1 g/dL
- Kappa free light chains (KFLC): 22.7 mg/dL
- Lambda free light chains (LFLC): 1.1 mg/dL
- Free light chain ratio (FLCR): 20.6
- Beta 2 Micro (B2M): 2.2

What regimen do you recommend for AB as second line therapy?

A) Carfilzomib, lenalidomide, dexamethasone (KRd)
B) Daratumumab, lenalidomide, dexamethasone (DRd)
C) Daratumumab, bortezomib, dexamethasone (DVd)
D) Carfilzomib, pomalidomide, dexamethasone (KPd)
E) Idecabtagene vicleucel (Abecma®)

Answer: B

Rationale: Anti-CD38 monoclonal antibody therapy is recommended for relapsed/refractory myeloma patients.

Given that disease responded to initial VRd, the patient should not be considered refractory to any drugs in that regimen.
Current side effects/concomitant diseases would be least impacted by this drug combination.
Dose of dexamethasone can be reduced in diabetic patients based on blood sugar control.

Question 4: Which of the following statements is **INCORRECT** about high dose melphalan conditioning?

A) High-dose melphalan is associated with high rates of emetogenicity and therefore should be given with a combination anti-emetic regimen (i.e. NK1 antagonist + 5HT3 antagonist + corticosteroid)
B) Patients with renal dysfunction (CrCl <30 mL/min, SCr >2.0 mg/dL, etc.) are recommended to receive full dose (200 mg/m^2) because melphalan is primarily metabolized by the liver
C) Most sources recommend a dose reduction to 140 mg/m^2 for patients with poor performance status, older age, and/or decreased LVEF

D) Nitrogen mustards, including melphalan, are associated with high rates of male infertility after treatment due to azoospermia in males
E) Treatment related MDS/AML is one type of secondary malignancy associated with alkylating agents. It is commonly seen 5-7 years after treatment and is associated with del5q or del7q
F) The dose limiting toxicity, mucositis, associated with high dose melphalan can be significantly reduced with the use of cryotherapy

Answer: B

Rationale: While melphalan is hepatically metabolized, MOST metabolism is done via spontaneous hydrolysis.
This gives melphalan it's short stability once prepared (1 hour).
Excretion of the drug is primarily renal (mostly as metabolites).
One study showed that a decrease in CrCl from 100 mL/min to 30 mL/min reduced clearance of melphalan by 28.2%.

Question 5: CD, a 52-year-old woman, presents with progressive history of worsening fatigue and bruising.

PMH:

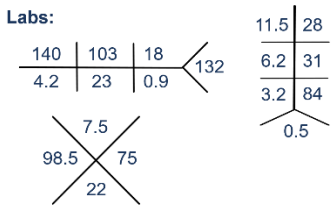
- History of breast cancer treated with lumpectomy and 4 cycles of doxorubicin/cytarabine followed by weekly paclitaxel x 12 doses. Completed about 2 years ago.

Vitals:

- Weight: 89 kg
- Blood pressure: 118/72

Current medications:
None

Labs:



Procedures:

- Bone marrow biopsy:
  - 47,XX,+8
  - Flow Cytometry: 60% abnormal blasts
  - Pathology: 54% blasts
  - Immunohistochemistry: 40-50% blasts

- Cytogenetics/FISH: t(11;19)(q23;p13.1), trisomy 8

Which of the following diagnosis/induction treatment options best fits CD?

A) Poor risk AML / Liposomal cytarabine + daunorubicin (CPX351; Vyxeos®)
B) Favorable risk AML by molecular mutation / Fludarabine + cytarabine + filgrastim + idarubicin (FLAG-Ida)
C) Poor risk AML / Cytarabine + doxorubicin/daunorubicin (7+3)
D) Intermediate risk AML / Azacitidine + Venetoclax
E) Favorable risk AML by cytogenetics / Cytarabine + doxorubicin/daunorubicin (7+3) + gemtuzumab ozogamicin (Mylotarg®)

Answer: C

Rationale: CD is considered Poor Risk because she has therapy related AML (history of anthracycline/topoisomerase II inhibitor with mutations showing 11q23/KMT2A rearrangement)

KMT2A – Lysine [K]-specific Methyltransferase 2A (previously called Mixed Lineage Leukemia gene or MLL)

Question 6: Which statement below is **MOST ACCURATE** about toxicities associated with cytarabine?

A) Conjunctivitis is a universal side effect of cytarabine and is seen in both dosing schemes.
B) Ara-C syndrome, characterized by fever, myalgia, and rash, is typically seen immediately after therapy begins.
C) Cerebellar toxicity seen with high-dose cytarabine is typically mild and does not require dose reductions.
D) GI toxicities are more commonly seen with conventional dosing of cytarabine.
E) Severe myelosuppression is more commonly associated with conventional dosing of cytarabine.

Answer: D

Rationale: Conventional cytarabine (low dose, continuous infusion; like that seen in 7+3) is more commonly associated with GI toxicities (nausea, vomiting, diarrhea, etc.).
GI toxicities can be seen at any dosing, but likely more common with prolonged exposure in conventional dosing.

Question 7: Which statement is INACCURATE regarding busulfan and cyclophosphamide conditioning for allogeneic stem cell transplant?

A) The dose of cyclophosphamide commonly used in this regimen has a high incidence of hemorrhagic cystitis and therefore requires uroprotection with mesna.
B) Busulfan is associated with seizures and requires seizure prophylaxis, except in instances when the busulfan is pharmacokinetically monitored and dose adjusted.
C) Busulfan is commonly associate with skin discoloration or hyperpigmentation, which typically occurs 2-3 week after therapy and can last for 2-3 months.
D) High-dose cyclophosphamide has been linked to cardiovascular toxicities such as atrial fibrillation, acute myocardial infarction, hypertension, palpitations, and cardiogenic shock.
E) Pharmacokinetic dosing of busulfan has resulted in lower rates of hepatic sinusoidal obstructive syndrome (SOS).

Answer: B

Rationale: Pharmacokinetic monitoring and dose adjustment does not lower incidence of seizures associated with busulfan. Seizure prophylaxis is required for all transplant dosing.
Original studies used phenytoin
Now levetiracetam is more commonly used.

Question 8: A patient with newly diagnosed, AML is seen for consult regarding options for induction therapy. Which of the following statements regarding targeted therapies is CORRECT?

A) Patients with FLT3 ITD mutations are recommended to receive midostaurin as part of their therapy but requires QTc monitoring due to risk of prolonged QT and TDP.
B) Young, fit patients with IDH1 mutation are recommended to receive ivosidenib as part of their induction, consolidation, and maintenance treatment.
C) Patients with FLT3 ITD mutations are recommended to receive quizartinib as part of their induction, consolidation, and maintenance treatment.
D) Patients with FLT3 TKD mutations are recommended to receive gilteritinib as part of their induction, consolidation, and maintenance treatment.
E) Elderly and/or unfit patients with IDH1 mutation are recommended to receive olutasidenib as part of their therapy.

Answer: C

Rationale: Quizartinib and midostaurin are both options for addition to intensive induction, consolidation, and maintenance for patients with FLT3 ITD mutations.
Quizartinib is NOT recommended or FLT3 TKD mutations (midostaurin remains the only option).

Question 9: A 43-year-old man presents to the ED with worsening fatigue and frequent bouts of epistaxis. CBC reveals a WBC of 20.3 and Hgb of 7.4. A bone marrow biopsy is performed with results suggesting an acute leukemia with t(15;17) by FISH. Which of the following statements regarding treatment for this patient is **INCORRECT**?

A) Arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) are the backbone of therapy for this leukemia diagnosis.
B) Prior to initiating therapy with ATO, patients should have an ECG to check for underlying QT prolongation.
C) Patients with high-risk APL, defined as a WBC at diagnosis >10, benefit from addition of anthracycline to their induction regimen.
D) Fever, shortness of breath, and increasing white blood count are signs that the disease is not responding to induction therapy.
E) Gemtuzumab ozogamicin can be used as an alternative to ATO in a patient with prolonged QTc.

Answer: D

Rationale: These are all signs and symptoms of APL differentiation syndrome (fever, shortness of breath, hypoxemia, pleural or pericardial effusions).

Close monitoring of volume overload and pulmonary status.
Initiate dexamethasone at first signs of respiratory compromise
10 mg BID for 3–5 days with a taper over 2 weeks
Consider interrupting ATRA therapy until hypoxia resolves.
For patients diagnosed with high-risk APL, initiate prophylaxis with corticosteroids
Prednisone 0.5 mg/kg/day
Dexamethasone 10 mg BID
Taper the steroid dose over several days

Question 10: Which statements below are **MOST ACCURATE** regarding polatuzumab vedotin (Polivy®)? **(Choose all that apply)**

A) Despite the increase in survival, pola-R-CHP has not been shown to be cost effective compared to RCHOP in newly diagnosed DLBCL.
B) Grade 3-4 hematologic side effects were significantly increased when adding polatuzumab to bendamustine + rituximab for R/R DLBCL.
C) Polatuzumab for R/R DLBCL significantly increased incidence of peripheral neuropathy, unlike its use for newly diagnosed DLBCL.
D) In trials, Pola-R-CHP utilized higher rates of primary prophylaxis of neutropenia, leading to lower rates of neutropenia/neutropenic fevers.

Answer: B and C

Rationale: Polatuzumab increased rates of all hematologic side effects when added to BR.
Anemia:
Pola-BR: 28.2% vs. BR: 17.9%
Neutropenia rates:
Pola-BR: 46.2% vs. BR: 33.3%
Thrombocytopenia rates:
Pola-BR: 41.0% vs. BR: 23.1%
Peripheral neuropathy was increased in Pola-BR (compared to BR) but was not increased in Pola-R-CHP (compared to RCHOP).
Pola-BR: 43.6% vs. BR: 7.7%
Pola-R-CHP: 52.9% vs. RCHOP: 53.9%
Likely related to the fact that in newly diagnosed patients, vincristine was replaced, which is known to cause neuropathy.

Question 11: EF if a 56-year-old man with a history of stage III diffuse large B-cell lymphoma (DLBCL). He was initially treated with 6 cycles of RCHOP with good response, however 6 months later he presented with fevers, chills, and fatigue and was found to be in relapse on PET scan. He was treated with 2 cycles of RICE followed by autologous stem cell transplant (ASCT). He now presents 5 years post ASCT with increased lymphadenopathy and fatigue with concerns of relapse.

SH:

- Works full time to support family.
- Lives with wife and 2 teenage children about 90 minutes from clinic.

Which treatment option would be the best fit for EF? (Choose all that apply)

A) Epcoritamab (Epkinly®)
B) Mosunetuzumab (Lunsumio®)
C) Glofitamab (Columvi®)
D) Axicabtagene ciloleucel (Yescarta®)
E) Haplo-identical stem cell transplant

Answer: C and D

Rationale: Glofitamab is approved for R/R DLBCL after 2 lines of therapy.
It's given weekly for 3 doses, then Q21days, which could be feasible for patients who live further from clinic.
Finite number of cycles (12).
Axicabtagene ciloleucel is also approved for R/R LBCL after 2 lines of therapy.
Large up-front time commitment for work-up, treatment, and monitoring.
No maintenance or long-term therapy necessary (until relapse).
Can 'quickly' return to normal routines.

Question 12: Which toxicities are seen more commonly in high-dose methotrexate regimens? **(Choose all that apply)**

A) Hepatotoxicity
B) Infection
C) Mucositis
D) Myelosuppression
E) Nephrotoxicity
F) Neurotoxicity
G) Pneumonitis

Answer: A,C,E and F

Rationale: Impaired function of folate cell transporters leads to excessive methotrexate accumulation in liver cells.
Risk Factors: Alcohol consumption; female; metabolic syndrome; kidney disease; older age.
Caused by cellular damage along entire GI tract.
Can be seen in lower doses if patient has poor clearance and extended exposure.
Risk Factors: Concurrent use of NSAIDs
Crystal nephropathy and direct tubular toxicity from methotrexate crystalizing.
Risk Factors: Age >49; concurrent use of salicylates, sulfonamides, NSAIDs, etc.; male, volume depletion; acidic urine.
Can manifest as encephalopathy, headache, seizure.
May be related to accumulations of adenosine and homocysteine in the CNS.

Risk Factors: concurrent CNS XRT; hypertension; female; higher cumulative dose.

Question 13: Which of the following is **MOST ACCURATE** regarding the role of leucovorin in high-dose methotrexate?

A) Leucovorin binds to and inactivates acrolein, a metabolite of methotrexate, preventing kidney damage.
B) Leucovorin provides a 'rescue' to healthy cells by providing a reduced form of folic acid necessary for DNA/RNA synthesis.
C) Leucovorin stabilizes the binding of methotrexate and thymidylate synthetase, enhancing the activity of methotrexate.
D) Leucovorin reduces the risk of hematologic toxicity.
E) Leucovorin provides a source of tetrahydrofolate that aids the body in eliminating methotrexate.
F) Leucovorin rapidly hydrolyzes the carboxyl-terminal glutamate residue from extracellular methotrexate into inactive metabolites.

Answer: B

Rationale: Methotrexate inhibits dihydrofolate reductase (DHFR) and thymidylate synthetase (TS), which are essential for DNA synthesis and repair.
Leucovorin, a reduced folate, can be used by healthy cells.
Malignant cells have a reduced capacity for the uptake of leucovorin, and thus do not gain this benefit

Question 14: GH is a 68-year-old female. She was diagnosed 3 months ago with chronic-phase CML and started treatment with imatinib. Her qPCR for BCR::ABL1 came back as 11%. What is your next step? **(Choose all that apply)**

A) Continue imatinib treatment and recheck at 6 months
B) Switch to ponatinib
C) Send for BCR::ABL1 kinase domain mutational analysis
D) Evaluate patient for adherence
E) Switch to dasatinib

Answer: A, D and E

Rationale: More information is technically needed to make the decision between continuing imatinib and switching to dasatinib.

Studies have shown that a steep decline to just over 10% at 3 months generally yields favorable outcomes by 6 months.
qPCR results from diagnosis and more clinical context would be necessary.

Adherence should ALWAYS be assessed if optimal response is not obtained with oral therapies.

Question 15: Which statement regarding BCR-ABL TKIs is **INACCURATE**?

A) T315I mutation is a contraindication for treatment with imatinib, bosutinib, dasatinib, and nilotinib.
B) Ponatinib is the preferred TKI for CML with T315I mutation in any phase.
C) The most common mechanism for resistance mutations to BCR-ABL TKIs is translocation.
D) Imatinib and ponatinib are the only BCR-ABL TKIs that can be taken without regard to gastric acid suppressant use.
E) Many of the toxicities associated with BCR-ABL TKIs are related to off-target effects.

Answer: C

Question 16: Which of the following statements about bispecific monoclonal antibodies (BsAbs) is INACCURATE?

A) Currently approved bispecific T-cell recruiting antibodies are only indicated in hematologic malignancies.
B) Variable fragment based BsAbs have higher tumor penetration and shorter half-life when compared to IgG based BsAbs.
C) CD3 is the immune cell bridge used most commonly for t-cell engaging due to low variance.
D) Blinatumomab (Blincyto®) is the only currently available BiTE® indicated for hematologic malignancies.

Answer: A

Rationale: This statement was true up until May 2024 when tarlatamab-dlle (Imdelltra®) was approved for small cell lung cancer.
Other BsAbs approved in solid tumors did not engage T-cells or other immune cells directly.
Amivantamab (EGFR + MET)
Drugs like tebentafusp are used in solid tumors, but are not *technically* antibodies (they are proteins)

Question 17: Which statement related to small molecules used in CLL management is MOST ACCURATE?

A) BCL2 G101V mutation has been implicated in clinical resistance to venetoclax.
B) BTK inhibitors are associated with hepatotoxicity while PI3K inhibitors are associated with bleeding.
C) Resistance to ibrutinib has been linked to mutations in BTK and PLCG2, which can be overcome by using an alternative BTK inhibitor such as acalabrutinib.
D) Both BTK inhibitors and PI3K inhibitors are associated diarrhea, but only PI3K inhibitors are associated with severe colitis.
E) Requirement for anticoagulation and use of gastric acid suppressants are contraindications to treatment with BTK inhibitors.

Answer: D

Rationale: BTK inhibitors have higher rates of diarrhea, however only PI3K inhibitors are associated with colitis.

Rates of severe colitis (Grade 3-4) is above 10% for idelalisib and duvelisib.
Idelalisib has a black box warning due to the risk of severe diarrhea and colitis.
Also, BBW for hepatotoxicity, pneumonitis, infection, and intenstinal perforation.

Question 18: IJ is a 41-year-old man with history of ALL. He has completed induction and one cycle of early intensification course and is getting labs prior to the repeat cycle of early intensification (based on CALGB 8811, Larson et al). His WBC returns as <0.1 and Hgb 6.2. Which genetic mutation/drug combo is the likely culprit for GH's pancytopenia? (More than one answer may be correct)

A) TPMT / 6-mercaptopurine
B) NUDT15 / cytarabine
C) UGT1A1*28 / pegaspargase
D) DPYD*2A / vincristine

Answer: A

Rationale: Deficiency in thiopurine methyltransferase (TPMT) can result in severe bone marrow suppression with 6-mercaptopurine (6MP). This is also a factor if using 6-thioguanine (6TG).

A heterozygous deficiency can require dose reductions of 30-70%.
A homozygous deficiency can require dose reductions of 90%.

Acute Lymphoblastic Leukemia : Ryan D. Cassaday, MD

Question 1: A 31-year-old woman presents with fatigue and easy bruising. A CBC reveals pancytopenia, including a white blood cell count of 1,900/μL, hematocrit 23%, and platelets 59,000/μL. A bone marrow exam confirms B-cell lymphoblastic leukemia, with flow cytometry showing over 90% of the cells are B lymphoblasts. Cytogenetics demonstrates the Philadelphia chromosome in all 20 metaphases. She is treated with induction chemotherapy including ponatinib, cyclophosphamide, vincristine, prednisone, and daunorubicin. Within 3 months of starting therapy, she achieves a complete remission based on morphology with no measurable residual disease (MRD) by flow cytometry or RT-PCR assays of bone marrow. She does not have a matched related or unrelated donor. What treatment approach should be recommended?

A) Blinatumomab alone
B) Bosutinib alone
C) Ponatinib plus consolidation and maintenance chemotherapy
D) Reduced-intensity haploidentical donor hematopoietic cell transplantation
E) Standard-intensity umbilical cord blood donor hematopoietic cell transplantation

Answer: C

Rationale: Ph+ ALL historically has a very poor prognosis when treated with conventional chemotherapy, so routine use of allogeneic hematopoietic cell transplantation was recommended in first remission. The addition of TKIs improves the initial complete remission rate and long-term outcome of patients with Ph+ ALL when combined with chemotherapy. Ponatinib-based approaches have called into question to the routine use of allogeneic transplantation in first remission, particularly if a complete molecular response (CMR) is achieved within 3 months of starting treatment. Blinatumomab consolidation improves survival for patients in MRD-negative remission, but this has only been studied in Ph- ALL.

Suggested Reading

- Jabbour E, Short NJ, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. *Lancet Haematol* 2018;5:e618-e627.

- Ghobadi A, Slade M, Kantarjian, et al. The role of allogeneic transplant for adult Ph+ ALL in CR1 with complete molecular remission: a retrospective analysis. *Blood* 2022;140:2101-2112.
- Jabbour E, Kantarjian HK, Aldoss I, et al. Ponatinib vs imatinib in frontline Philadelphia chromosome–positive acute lymphoblastic leukemia: a randomized clinical trial. *JAMA* 2024;331:1814-1823.

Question 2: A 61-year-old man presents with a white blood cell count of 38,000/μL (of which 86% are B lymphoblasts by flow cytometry), a hematocrit of 38%, and a platelet count of 110,000/μL. Cytogenetics demonstrates a complex karyotype in 19 of 20 metaphases. He is treated with induction chemotherapy according to the E1910 regimen: daunorubicin, vincristine, and dexamethasone, followed by cyclophosphamide, mercaptopurine, and low-dose cytarabine. He achieves a complete remission based on morphology and cytogenetics, but measurable residual disease (MRD) is detected by flow cytometry. He then receives Intensification, consisting of methotrexate and pegaspargase. A repeat bone marrow examination now shows persistent/refractory disease, with 12% blasts by morphology. He does not have a matched sibling. What should be recommended now?

A) High-dose cytarabine based salvage chemotherapy
B) Blinatumomab
C) Ponatinib
D) Nelarabine
E) Reduced-intensity unrelated donor hematopoietic cell transplantation

Answer: B

Rationale: Complex karyotype (typically defined as 5 or more chromosomal abnormalities) and persistence of MRD are both associated with poor prognosis in ALL, so it is no great surprise that his patient suffered a relapse of his ALL. Blinatumomab, the CD3-CD19 bispecific T-cell engager, is approved for treatment of relapsed/refractory Ph- B-cell ALL, and it was shown to be superior to investigator's choice of salvage chemotherapy (including high-dose cytarabine based options) in an international phase 3 randomized controlled trial (the TOWER study). Ponatinib would only be considered in Ph+ ALL. Nelarabine is approved only for T-ALL. While reduced-intensity allogeneic transplantation would be a consideration for this patient as a longer-term goal, it would typically only be offered to patients in remission (e.g., after response to blinatumomab).

Suggested Reading:

- Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukemia: a multicenter, single-arm, phase 2 study. *Lancet Oncol* 2015;16:57-66.
- Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 2017;376:836-847.
- Litzow MR, Sun Z, Mattison RJ, et al. Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults. *N Engl J Med* 2024;391:320-333.

Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Lymphoma (SLL) & Hairy Cell Leukemia : Mazyar Shadman, MD, MPH

Question 1: A 74-year-old woman with a 7-year history of CLL returns to the clinic for follow-up. Three years ago, patient was treated with 6 cycles of fludarabine cyclophosphamide and rituximab. In the past 4 months, she has been experiencing worsening anemia and thrombocytopenia. Her blood work 2 weeks ago showed WBC 45,000cell/uL with 90% lymphocytes, hematocrit 32% and a platelet 55,000/uL. Patient's comorbidities include a mechanical mitral valve for which she has been on warfarin therapy for 7 years, hypertension and diabetes. You performed a bone marrow biopsy 2 weeks ago which showed 80% involvement by CLL cells by flow cytometry and morphology. The CLL FISH only showed 13q14 deletion. There is no evidence of myelodysplastic changes.

Which one of the following treatment options is recommended?

A) Start single agent acalabrutinib or zanubrutinib and continue until progression
B) Start treatment with Pirtobrutinib and continue until progression
C) Start combination venetoclax and rituximab and continue for 2 years
D) All 3 options are reasonable.

Answer: C

Rationale: Acalabrutinib and zanubrutinib are effective treatment for all lines of treatment including the second line. However, concurrent use of BTK inhibitors (ibrutinib or acalabrutinib or pirtobrutinib) and warfarin can potentially increase the bleeding risk (including intracranial bleeding). Other anticoagulation methods (e.g.: DOACs) don't seem to be feasible given the indication for anticoagulation (mechanical valve). Combination of venetoclax and rituximab (given for 2 years) was superior to BR in the relapsed setting in the MURANO study and is considered one of the standard treatment choices in this setting. Please note that there is drug-drug interaction between venetoclax and warfarin and close monitoring of INR is recommended.

Question 2: A 64-year-old man with history of chronic lymphocytic leukemia with normal cytogenetics returns to the clinic for clinical follow-up. Five years ago, he received chemo-immunotherapy with FCR and has been in remission until 2 months ago when he presented with worsening lymphadenopathy, an absolute lymphocyte count of 42,000 cell/uL, hematocrit 34% and platelet count of 82,000/uL. He was started on acalabrutinib 100 mg BID. Today, he reports some improvement in the lymphadenopathy but his lymphocyte count is now increased to 84,000 cell/uL. His hematocrit currently is 36% and the platelets count is 95,000/uL.

What is the next best step in management of this patient?

A) Continue treatment and re-evaluate the patient in a month
B) Switch to zanubrutinib reassess in a month
C) Switch to pirtobrutinib reassess in a month
D) Switch the treatment to venetoclax (start the ramp-up schedule) and repeat blood work in a month
E) Switch to chemo-immunotherapy with Bendamustine and rituximab and avoid B-cell receptor (BCR) inhibitors in future.

Answer: A

Rationale: Lymphocytosis is expected after treatment initiation with BTK and Pi3K inhibitors. Given the improvement of HCT and platelet, treatment should be continued with no changes.

Question 3: As 65-year-old man with CLL who has been on ibrutinib for 4 years for high-risk CLL (mutated TP53) presents with enlarging cervical nodes for more than a month. CBC shows rising lymphocytes with an ALC 10,000 compared to 3,500 4 months ago. A PET scan shows that all lymph nodes have FDG uptake 2-4. An excisional LN biopsy shows CLL with no evidence of histologic transformation. Mutation an analysis of the CLL cells shows mutation of C481S.

Which one of the following actions is recommended in this patient?

A. Switch to second generation BTKi, acalabrutinib
B. Switch to second generation BTKi, Zanubrutinib
C. Start venetoclax and anti-CD20 antibody
D. Start Pirtobrutinib
E. Either #2 or #3
F. All options all reasonable. Patient's comorbidities will help is deciding between the above options

Answer: E

Rationale: Second generation BTKis like acalabrutinib and zanubrutinib have the same binding site and mechanism of action as ibrutunib. Mutations affecting the C481 residue of BTK disrupt drug binding and have been characterized as the most common mechanism of resistance for both ibrutinib and acalabrutinib. Therefore, use of acalabrutinib and zanubrutinib are not recommended in patients with the mutation. Venetoclax and anti-CD20 antibody combination would be Pirtobrutinib is another reasonable option. Currently approved for patients after prior treatment with covalent BTKi and BCL2 inhibitor. Therefore, it is currently (October 2025) considered off-label although listed on NCCN guidelines for this setting based on the results of BRUIN-321 study.

Chronic Myeloid Leukemia : Cristina M. Ghiuzeli, MD

Question 1: BB is a 75-year-old female with history of Atrial Fibrillation on chronic anticoagulation with Apixaban, chronic phase CML treated with Dasatinib 100mg daily. Major molecular response (BCR-ABL1 transcripts less than 0.1%) is achieved at 10 months. At her 12 month visit, the patient complains of a mild intermittent cough, especially after exertion. On exam, breath sounds on the right side are decreased halfway up the lung field.

What is the next step in her treatment?

A) Stop dasatinib and start bosutinib 500mg daily
B) Decrease dasatinib to 50mg daily, continue to monitor PCR every 3 months
C) Stop dasatinib and start nilotinib at 300 mg twice daily
D) Stop dasatinib and monitor PCR's more frequently, every month for the first year

Answer: B

Rationale: One of the most common serious side effects of dasatinib is pleural effusion. This is particularly common in older patients, and the cough and decreased breath sounds on exam are signs of it. This occurs much less frequently with decreased dose dasatinib, thus answer C is correct. For nilotinib irreversible complications include cerebrovascular, cardiovascular, and peripheral arterial occlusive events –this patient has A fib, thus she would be at increased risk for cardiovascular complications. Stopping Dasatinib is not a good choice because it is too early to do so.

Question 2: TS is a 32-year-old woman who is 10 weeks pregnant. On a routine blood work, she was found to have a white cell count of 50k/ul with left shift and 1% blasts, hemoglobin 10g/dl, platelet count of 120k/ul. On further work up, a PCR for p210 for BCR-ABL was positive at 10 IU.

Appropriate treatment strategies include which of the following?

A) Start Imatinib 400mg once daily immediately
B) Start Imatinib 400mg once daily at the start of the second trimester, after organogenesis is complete
C) Start a second generation tyrosine kinase inhibitor, either dasatinib or bosutinib
D) Start interferon injections
E) Do not start any treatment during pregnancy

Answer: D

Rationale: TKI's are not safe during pregnancy, as they can cause miscarriages and fetal abnormalities, thus answers A, B and C are wrong. The white blood cell count is high, thus option E of not starting any treatment is not a good options. Interferon is the only safe treatment during pregnancy.

Acute Myeloid Leukemia : Mary-Elizabeth M. Percival, MD, MS

Question 1: A 55-year-old woman with a previous history of stage 2 breast cancer treated with chemotherapy (doxorubicin, cyclophosphamide, and paclitaxel) and radiation 2 years prior to admission presents to the emergency department with worsening dyspnea on exertion and gum bleeding. Laboratory studies are notable for a white blood cell count of 55,000/microliter, hemoglobin of 7.5g/dl, and platelets of 15,000/microliter. She is diagnosed with AML based on the presence of 65% myeloid blasts. Which of the following is the most likely mutation to be identified on subsequent molecular and cytogenetic testing of the blasts?.

A) t(9;11)
B) ASXL1
C) t(16;16)
D) trisomy 8
E) FLT3-ITD

Answer: A

Rationale: This patient has therapy-related AML based on her prior receipt of chemotherapy and radiation. Some patients with therapy-related AML will have certain canonical chromosome abnormalities. In particular, patients who have received prior anthracycline therapy, such as doxorubicin for breast cancer, are at an increased risk of developing rearrangements in the chromosome locus 11q23, which involve the KMT2A gene. Therefore, the correct answer to this question is option A. The other cytogenetic and molecular abnormalities can all occur in patients with therapy-related AML, but they are less common than t(9;11).

Question 2: A 55-year-old woman with a previous history of stage 2 breast cancer treated with chemotherapy (doxorubicin, cyclophosphamide, and paclitaxel) and radiation 2 years prior to admission presents to the emergency department with worsening dyspnea on exertion and gum bleeding. Laboratory studies are notable for a white blood cell count of 55,000/microliter, hemoglobin of 7.5g/dl, and platelets of 15,000/microliter. She is diagnosed with AML based on the presence of 65% myeloid blasts. Cytogenetics confirm t(9;11). She receives induction followed by an allogeneic hematopoietic cell transplant. Unfortunately, she relapses with circulating myeloid blasts one year post transplant. Which of the following is the most appropriate next treatment?

A) Revumenib
B) Ivosidenib
C) Gilteritinib
D) Asciminib
E) Sorafenib

Answer: A

Rationale: This patient was diagnosed with a therapy-related AML in the setting of prior chemotherapy and radiation for breast cancer. She appears to have intermediate-risk disease based on the t(9;11) translocation identified at diagnosis using the European LeukemiaNet 2022 criteria. Rearrangements in the chromosome locus 11q23 involve the KMT2A gene. At the time of relapse, it would be appropriate to treat her with a targeted therapy, and the first menin inhibitor (revumenib) was approved for relapsed/refractory (R/R) acute leukemia with a KMT2A rearrangement in 2024. Option A is the correct answer choice.

Ivosidenib is an IDH1 inhibitor, which is approved for the treatment of IDH1-mutated AML in the upfront and R/R settings. Gilteritinib is a FLT3 inhibitor, which is approved for the treatment of FLT3-mutated AML in the R/R setting. Asciminib is a newly approved tyrosine kinase inhibitor used for the treatment of CML. Sorafenib is a multikinase inhibitor with some activity against FLT3, but it is not approved for the treatment of AML.

Myelodysplastic Syndromes : Jacob Appelbaum, MD, PhD

Question 1: 77yM with fatigue. CBC shows WBCs of 3k/uL, Hg 7g/dL, Plts 110/uL. He has received 4 transfusions in the prior 3 months. A marrow biopsy showed 15% erythroid dysplasia without ring sideroblasts. Blasts were not increased.

Cytogenetics showed 46XY, del(5q) in 12 of 20 metaphases. EPO level is 300 mU/mL. His brother is an HLA match.

Which of the following are appropriate initial therapies?

A) Luspatercept 5mg daily
B) Imetelstat 7.5mg/kg IV q4 wks
C) Allogeneic transplantation
D) Azacytidine 75mg/m2
E) Lenalidomide
F) Recombinant erythropoietin stimulating agents (epoetin alfa)
G) E or F

Answer: G

Rationale: Patients with del5q were excluded from IMerge, Medalist and Commands trials evaluating imetelstat and luspatercept.
Azacytidine improves hematopoiesis in some patients, but exhibits a survival advantage only in high risk patients.
Allogeneic transplant should be reserved for high risk patients. Lenalidomide improved erythropoiesis and reduced transfusion burden among patients with del5q, many of whom were ESA refractory. E or F are appropriate.

Question 2: 77yM with fatigue. CBC shows WBCs of 3k/uL, Hg 7g/dL, Plts 110/uL. He has received 4 transfusions in the prior 3 months. A marrow biopsy showed 15% erythroid dysplasia without ring sideroblasts. Blasts were not increased.

Cytogenetics showed **46XY, -Y** in 12 of 20 metaphases. EPO level is 300 mU/mL. His brother is an HLA match.

Which of the following are appropriate initial therapies?

A) Luspatercept 5mg daily
B) Imetelstat 7.5mg/kg IV q4 wks
C) Allogeneic transplantation
D) Azacytidine 75mg/m2
E) Lenalidomide
F) Recombinant erythropoietin stimulating agents (epoetin alfa)
G) E or F

Answer: A

Rationale: Luspatercept and Imetelstat were evaluated in non-del5q patients, but imetelstat excluded patients likely to respond to EPO. The Commands trial showed superior transfusion independence rates compared to EPO.

Myeloproliferative Neoplasms : Anna B. Halpern, MD

Question 1: A 67-year-old man is evaluated during follow-up consultation after thrombocythemia is discovered

incidentally on a routine health maintenance examination. His medical history is notable for

depression with history of suicidal ideation, and he takes sertraline only.

On physical examination, he is afebrile, blood pressure is 115/72 mm Hg, pulse rate is 72/min, and

respiration rate is 18/min. Cardiac evaluation reveals a regular rate and rhythm with no murmurs.

Results of laboratory studies show a hemoglobin level of 15 g/dL (150 g/L), leukocyte count of

5600/μL (5.6 × 109/L), and platelet count of 770,000/μL (770 × 109/L). Bone marrow biopsy shows

megakaryocytic proliferation without fibrosis and molecular testing finds a JAK2 V16F mutation,

consistent with ET.

Question: Which of the following is the most appropriate treatment?

A. Pegasys plus low-dose aspirin
B. Hydroxyurea plus low-dose aspirin
C. Ruxolitinib
D. Warfarin
E. Observation

Answer: B

Rationale: Pegasys is contraindicated due to history of SI. Ruxolitinib is not approved for ET. 4/5 are not enough- cytoreduction is required due to Age >60

Question 2: A 76-year-old woman had a five-year history of CALR-mutated intermediate-2 risk myelofibrosis. For the past 2 years she has been on

ruxolitinib with improvement in constitutional symptoms and reduction in spleen size. However over the last few months, she has had

worsening early satiety, LUQ fullness and night sweats. Abdominal ultrasound confirms increase in spleen volume 30% from prior. She is not a

candidate for stem cell transplant, and you would like to switch her to fedratinib.

Question: Which laboratory values would you like to confirm prior to switching?

A. Hgb >10 g/dL, folate >4 ng/ml
B. Platelet >50,000/µL, b12 (cobalamin)> 180 pg/ml
C. Platelet <50,000/µL, folate >4 ng/ml
D. Hgb >10 g/dL, b1 (thiamine) >70 nmol/L
E. Platelet >50,000/µL, b1 (thiamine) >70 nmol/L

Answer: E

Rationale: Fedratinib is contraindicated in patients with history of wernicke's encephalopathy or thiamine deficiency so this must be checked, It is approved only for plts >50

Smoldering Myeloma & MGUS : Mary Kwok, MD

Question 1: A 62 year old patient is referred to you for evaluation of an IgG kappa monoclonal gammopathy that was identified after routine labs were notable for an elevated total protein.
Labs are notable for the following:
WBC 4.5 x 10(3)/microL
Hgb 13.7 g/dL
Hct 39%
Platelets 178
Creatinine 0.71 mg/dL
Calcium 9 mg/dL
Total protein of 9 g/dL (normal 6 - 8.2 g/dL)
Albumin 4.1 g/dL
SPEP identifies a monoclonal protein, measuring 1.9 g/dL
Serum immunofixation identifies an IgA kappa monoclonal protein
Kappa: 7 mg/dL (normal 0.33 - 1.94 mg/dL)
Lambda 0.3 mg/dL (normal 0.57-2.63 mg/dL)
Kappa/Lambda 23

A whole body low dose CT scan demonstrates no osseous lesions or compression fractures.

A bone marrow biopsy is performed, demonstrating 30% plasma cells by CD138 IHC, kappa restricted by flow cytometry. FISH identifies gain of chromosomes 5, 9 and 15, but is otherwise normal. You identify that this patient has smoldering myeloma.

A) This patient has low risk smoldering myeloma, recommend observation
B) This patient has intermediate risk smoldering myeloma, recommend observation
C) This patient has high risk smoldering myeloma, recommend observation
D) This patient has high risk smoldering myeloma, recommend treatment with lenalidomide
E) C and D

Answer: E

Question 2: A 55 year old patient is referred to you for evaluation of a new monoclonal gammopathy, identified during a workup for mild CKD with proteinuria.
Labs are notable for the following:
WBC 6 x 10(3)/microL
Hgb 14 g/dL
Hct 40%
Platelets 250
Creatinine 1.4 mg/dL
Calcium 9 mg/dL
Total protein of 9 g/dL (normal 6 - 8.2 g/dL)
Albumin 4.1 g/dL
Urine spot prot/creatinine ratio: 8
SPEP identifies an monoclonal protein, measuring 0.7 g/dL
Serum immunofixation identifies an IgG lambda monoclonal protein
Kappa: 1.45 mg/dL (normal 0.33 - 1.94 mg/dL)
Lambda 30.54 mg/dL (normal 0.57-2.63 mg/dL)
Kappa/Lambda 0.05
A whole body low dose CT scan demonstrates no osseous lesions or compression fractures.
A bone marrow biopsy is performed, demonstrating 10% plasma cells by CD138 IHC, kappa restricted by flow cytometry. Congo red stain is positive for amyloid deposition. FISH identifies t(11;14) but is otherwise normal.

Which of the following is the most appropriate next step?
A) Initiate therapy with CyBorD+daratumumab
B) Type the amyloid with liquid chromatography tandem mass spectrometry (LC MS/MS)
C) Monitor with routine labs in 3 months
D) Initiate therapy with RVD

Answer: B

Question 3: The above patient was evaluated with LC MS/MS which demonstrated AL (lambda-type) amyloidosis. There is no significant cardiac involvement by TTE and NT-ProBNP and troponin are in normal range.
Which of the following should you recommend now?

A) Initiate therapy with CyBorD+daratumumab
B) Initiate therapy with RVD
C) Initiate therapy with CyBorD
D) Proceed with autologous stem cell transplant

Answer: A

Newly-Diagnosed Myeloma : Kara Cicero, MD, MPH

Question 1: A 54yo woman presents for a second opinion. Her prior Onc team recently diagnosed her with MM and are recommending treatment with dara-RVd. Upon reviewing her records, you notice that her hemoglobin, creatinine and calcium are within normal limits. A PET/CT showed no evidence of plasmacytomas or skeletal lesions, and a whole-body MRI does not show any focal lesions. Bone marrow biopsy revealed 17% plasma cells with diploid cytogenetics and FISH studies were unrevealing. SPEP with IF reveals an M-protein of 2.5 g/dL IgG kappa and her free kappa/lambda ratio is 50.

What is her diagnosis?

A. Multiple myeloma
B. Smoldering myeloma
C. MGUS
D. Waldenstrom's macroglobulinemia

Answer: B.

Rationale: Smoldering myeloma. Since she has >10% plasma cells in her BM, she at least has smoldering myeloma and not MGUS. However, there is no evidence of a myeloma defining event ("SLIM-CRAB"): >60% bone marrow plasmacytosis, >100 free light chain ratio (with involved free light chain >10 mg/dL), >1 focal lesions on MRI, hypercalcemia, renal insufficiency, anemia, or lytic lesions/plasmacytomas on PET/CT

Question 2: A 71yo man has routine yearly labs drawn by his PCP. On his CMP, his total protein is 9.8 g/dL and albumin is 3.5 g/dL. Because of this high protein/albumin ratio, an SPEP with IF is ordered, which shows an IgG kappa M-protein of 2.5 g/dL. Free kappa/lambda light chain ratio is 35. A 24 hr urine collection reveals Bence-Jones protein levels of 400 mg/24 hrs.
The patient is referred to see a Hematologist/Oncologist. A bone marrow biopsy is performed and reveals 8% plasma cells and normal cytogenetics. His Hgb, creatinine, calcium, and PET/CT are all normal. What therapy would you offer?

A. Melphalan, bortezomib, prednisone
B. Lenalidomide, bortezomib, dexamethasone
C. Bortezomib and dexamethasone
D. Observation

Answer. D.

Rationale: Observation. He meets the criteria for MGUS. Observation should be recommended. MGUS is found in 4-8% of people who are ≥50 years old and 13% of those >80 years old. Characterized by presence of M-protein, <10% plasma cells in the BM, and absence of myeloma-defining features. Annual risk of transformation to myeloma is ~1%.

Question 3: A 68yo man presents with a new diagnosis of myeloma. His creatinine is 3.9 mg/dL, calcium is 9 mg/dL, and Hgb is 9.8 g/dL. PET/CT shows lytic lesions throughout his body. SPEP shows an IgG lambda M-protein of 5.2 g/dL and 24 hr UPEP/IF reveals 365 mg of lambda Bence-Jones protein. His serum B2 microglobulin is 5.0 mg/dL.
A bone marrow biopsy shows 65% plasma cells. Cytogenetics/FISH reveals a 13q deletion. LDH is normal. What therapy do you offer?

A. Lenalidomide and dexamethasone
B. Bortezomib and dexamethasone +/- cyclophosphamide
C. Lenalidomide, melphalan, dexamethasone
D. Melphalan, prednisone, thalidomide

Answer. B.

Rationale: Bortezomib and dexamethasone +/- cyclophosphamide. CyBorD is the preferred regimen in the treatment of myeloma patients presenting in renal failure.
This is not entirely true – we still recommend dara-RVd as front line (and lenalidomide is renally-dosed), but often times because of urgency with renal insufficiency cannot start dara-RVd immediately and so therefore start CyBorD inpatient because that is the only option available to start immediately; maybe better choices would be:

A. Outpatient initiation of lenalidomide and dexamethasone
B. Urgent inpatient initiation of cyclophosphamide, bortezomib, and dexamethasone
C. Outpatient initiation of daratumumab, pomalidomide, dexamethasone
D. Urgent inpatient initiation of high-dose melphalan

Question 4: A 76yo woman presents for a 2nd opinion. She was diagnosed with multiple myeloma 2 months prior after routine labs found an acute kidney injury. Serum markers showed an IgA kappa M-spike 1.14 g/dL, kappa FLCs 1,280 mg/dL, lambda FLCs 1.01 mg/dL. CT imaging identified compression deformities at L4 and L2. Bone marrow biopsy showed 80-90% plasma cells. Karyotype is complex. FISH shows t(14;16). Kidney biopsy showed light chain cast nephropathy. [deleted this sentence – we would ideally start quad and not CyBorD]. She is very active, exercising regularly and walks several miles per day and has no significant comorbidities.

Which of the following would you recommend as first-line therapy?

A. CyBorD (cyclophosphamide, bortezomib, dex)
B. dara-Rd (daratumumab, lenalidomide, dex)
C. isa-VRd (isatuximab, bortezomib, lenalidomide, dex)
D. KRD-PACE (carfilzomib, lenalidomide, dex, cisplatin, doxorubicin, cyclophosphamide, etoposide)

Answer. C.

Rationale: isa-VRd (isatuximab, bortezomib, lenalidomide, dex). Quad therapy is preferred among transplant ineligible patients with NDMM who are fit and able to tolerate it based on IMROZ, BENEFIT, and CEPHEUS trials.

<u>Relapsed/Refractory Myeloma & Amyloidosis : Rahul Banerjee, MD, FACP</u>

Question 1: Cytokine release syndrome following CAR-T therapy is almost universally marked by which of the following signs?

A) Delirium
B) Anasarca
C) Fever
D) Hepatic veno-occlusive disease

Answer: C. Fever

Rationale: Over 99% of cases of cytokine release syndrome (CRS) following chimeric antigen receptor T-cell therapy will involve fevers. Grade 1 CRS comprises fevers alone, while higher-grade CRS involves other signs such as hypotension or hypoxia. Delirium can occur with immune effector cell-associated neurotoxicity syndrome (ICANS). Anasarca and veno-occlusive disease would not be expected.

Question 2: Talquetamab is an approved bispecific antibody targeting GPRC5D (on myeloma and other cells) and CD3 on T cells. Which of the following off-tumor on-target toxicities may be commonly expected?

A) Blurred vision
B) Peripheral neuropathy
C) Dygeusia
D) Renal thrombotic microangiopathy

Answer: C. Dygeusia

Rationale: Talquetamab targets GPRC5D, which is found on myeloma cells as well as keratinized epithelial cells in the skin (typically palms), nails, and tongue. Skin/nail and tongue toxicities are thus quite common with talquetamab. In particular, over half of patients receiving talquetamab in trials and real-world experience have developed dysgeusia (taste changes) and a significant minority will lose over 10 pounds of weight. Dose de-escalation and supportive care are thus important with talquetamab. Belantamab mafodotin can cause blurred vision, bortezomib can cause peripheral neuropathy, and carfilzomib can cause thrombotic microangiopathy involving the kidneys. These would not be expected with talquetamab.

Friday, October 10

Inherited & Acquired Marrow Failure : Sioban B. Keel, MD

Question 1: 22 yo male was referred for hematopoietic stem cell transplantation for MDS characterized by monosomy 7 (IPSS-R high risk). The patient's 24 year-old sister is reportedly healthy apart from recurrent herpes stomatitis. She is a 10/10 HLA allele-match to the patient. He has no other siblings. His mother is 44 years of age and has mild thrombocytopenia. His father is 51 years of age and is healthy.

Which of the following studies is most likely to establish a diagnosis?

A) Genetic testing of peripheral blood
B) Telomere length testing
C) Bone marrow aspirate and biopsy
D) Genetic testing of cultured skin fibroblasts
E) Platelet aggregometry

Answer: D

Rationale: This patient presents with a high-risk MDS characterized by monosomy 7 at a young age (22 years-old). Additionally, his family history is notable for a mother with thrombocytopenia and a sister with recurrent herpes stomatitis. These findings suggest GATA2 deficiency. Inherited and de novo heterozygous germline mutations in the hematopoietic transcription factor, GATA2, cause this pleotropic autosomal dominant genetic disorder characterized by cellular immunodeficiency (complicated frequently by viral and disseminated nontuberculous mycobacterial infections) and a high risk for myeloid malignancy1. Hematopoietic stem cell transplantation offers the only cure for MDS/AML and for reconstitution of the immune system in this syndrome. GATA2 deficiency underlies ~ 7% of pediatric and adolescent myelodysplastic syndrome patients and is particularly enriched among those whose disease is characterized by monosomy 7 (37%, all ages, 72% of adolescents)

Question 2: 21 yo male referred for mild chronic thrombocytopenia and macrocytic anemia. Serum B12 and folate levels normal. PMH notable for recurrent perineal warts. Brother was diagnosed with monosomy 7 MDS at 15 yo and is now two years post an HLA-matched sib HSCT. Mother is 45 yo and has mild thrombocytopenia. Exam was unremarkable.

Lab		Reference Range
HGB	10.8 g/dL	12-16 g/dL
MCV	104 fL	80-100 fL
WBC	5300/mL	4300-10,000/mL
ANC	4000/mL	1800-7,000/mL
Lymphocytes	1100/mL	1000-4800/mL
Monocytes	0/mL	0-800/mL
PLT	125,000/mL	150,000-400,000/mL

Marrow - hypocellular for age with normal blast percentage and atypical megakaryocytes.

No immunophenotypic abnormalities.

Routine karyotype 46, XY.

Which of the following studies is most likely to establish a diagnosis?

A) Platelet aggregometry
B) Genetic testing
C) Serum folate and B12 levels
D) Chromosomal microarray
E) Telomere length testing

Answer: B

Rationale: This patient has a significant family history of cytopenias and myeloid malignancy suggestive of an autosomal dominant inherited myeloid leukemia predisposition syndrome. Genetic testing for an inherited syndrome should be considered. Panel-based next generation sequencing methodologies allow testing for many of these syndromes simultaneously. The methodologies employed (sensitivity and genomic coverage) and interpretation of results remains complex and requires careful consideration of both assay design and interpretation of results. Additionally, when clinically possible, cultured skin fibroblasts are the recommended DNA source for germline testing in order to exclude somatic mutations and to avoid false negatives due to peripheral blood/marrow somatic mosaicism.

Benign White Cell Disorders : Lindsay Hammons, MD

Question 1: A 34-year-old recent traveler to rural India has an absolute eosinophil count of 1,800/mm^3. He denies allergies. Which of the following is the most appropriate next step?

A) Bone marrow biopsy
B) Begin corticosteroids
C) Peripheral blood smear and stool O&P exam
D) CT scan of chest and abdomen

Answer: C

Rationale:

(A) Patient has travel history to a rural area in Asia with high eosinophilia count. Would like to avoid more invasive testing first. Generally we do peripheral labs and other easy-to-collect studies before proceeding to a bone marrow biopsy. If we find a reason for which to treat the eosinophilia, no invasive procedure is needed.

(B) We should diagnose the etiology of eosinophilia prior to starting treatment, as steroids may dampen the eosinophilic response and mask the evolution of the underlying cause OR we might need treatment other than steroids OR it could alter the appearance of the bone marrow biopsy. Additionally, there is no rush to start treatment early in this case, as there is no mention of symptoms/signs of end organ damage.

(C) Travel to rural area in Asia exposes patients to parasites, which can lead to eosinophilia. Other good infectious disease initial tests include peripheral blood analysis for Toxoplasma and Strongyloides.

(D) Eosinophilia does not always cause end organ damage, although it can if it is present for a long period of time – mostly in the heart, liver, and lungs. Additionally, unless there is an underlying lymphoma or solid malignancy, lab studies/PFTs are more

telling of end organ damage. Aspergillosis can also show up in the lungs, so important to look for in certain cases, but the patient is not overtly showing any evidence of pulmonary symptoms, so O&P would be the better answer.

Question 2: A 30-year-old healthy African American man presents for a routine check-up. His CBC reveals a WBC count of 3.2 × 10^9/L and an absolute neutrophil count (ANC) of 1.1 × 10^9/L. He denies any symptoms and has no history of recurrent infections. Physical exam is unremarkable. Repeat labs are similar. Which of the following best explains this finding?

A) Early presentation of chronic neutrophilic leukemia
B) Viral suppression of the bone marrow
C) Drug-induced neutropenia
D) ADAN due to ACKR1 gene variant
E) Idiopathic aplastic anemia

Answer: D

Rationale:

(A) Usually CNL presents with B symptoms, and the patient is generally asymptomatic. He does not have recurrent infections, unintentional weight loss, early satiety, or fevers/chills, night sweats or lymphadenopathy. A flow cytometry could further differentiate this diagnosis on peripheral blood. Additionally, absolute neutrophil count would generally be HIGH in CNL, as opposed to low.

(B) Again, patient is having no signs/symptoms of infection. No overt exposures to infections are stated. Many times, if viruses are affecting the marrow significantly, there would be signs/symptoms of that infection (not always, but many times). Due to the ethnic background of the patient, answer (D) is the better answer.

(C) No particular drugs were discussed in this question. In clinic, it is important to take a detailed medication history, as well as ask about any changes in medications and be able to correlate those with any new presentation of neutrophilia, as able. In this case, the overt statement of the patient's ethnicity and lack of symptoms points more to answer (D).

(D) ADAN – or ACKR1/DARC associated neutropenia – fits with this clinical case. Lack of symptoms/signs of B symptoms or infectious causes, or recurrent infections, as well as ethnic background. ADAN is generally found in those from West African, Middle Eastern and Yemenite Jewish decent.

(E) This diagnosis is only possible to prove on bone marrow biopsy. Additionally, aplastic anemia generally must have at least 2 lines of cytopenias, and this patient only has neutropenia.

Thalassemia & Hemoglobinopathies : Kleber Yotsumoto Fertrin, MD, PhD

Question 1: A 34yo F is diagnosed with stage IA Hodgkin's disease and is noted to have anemia. CBC shows (reference ranges):

Parameter	Result	Reference range
WBC (x103/µL)	6.7	4.0-10.0
RBC (x106/µL)	4.60	4.00-5.10
Hgb (g/dL)	11.0 (L)	12.0-16.0
Hct (%)	32.0 (L)	36.0-45.0
MCV (fL)	72 (L)	80-99
MCH (pg)	22 (L)	28-32
PLT (x103/µL)	220	150-450

Hgb HPLC: HbA 97%, HbA2 2.5%, HbF<1%. Ferritin and transferrin saturation are pending.

What is the most likely diagnosis?

A) Alpha thalassemia trait
B) Beta thalassemia trait
C) Anemia of inflammation
D) Needs ferritin and transferrin saturation to distinguish iron deficiency and anemia of inflammation

Answer: A

Rationale: Beta thalassemia trait causes HbA2 elevation, typically above 4%, not a decrease. Decreased HbA2 can be found in iron deficiency or alpha thalassemia. Iron deficiency or anemia of inflammation restrict iron available to the bone marrow and therefore cause low RBC counts, particularly if enough to cause significant microcytosis. In this case, RBC counts are normal despite microcytosis and anemia. Therefore, the only correct option is alpha thalassemia trait.

Question 2: A 23-year-old female with sickle cell anemia is admitted for vaso-occlusive crisis and hemoglobin 5.5g/dL. She is discharged after proper pain control and transfusion of 2 packed RBC units. She returns 10 days later reporting new acute pain, fatigue, and dark urine, with Hb 4.5g/dL. On exam, there is extreme pallor and jaundice, but she is hemodynamically stable. LDH increased from 500 to 980 U/L, DAT and screen are both positive, eluate is positive for an anti-C.

What is the recommended treatment?

A) Transfuse 2 C-negative RBC units
B) Start eculizumab
C) Start corticosteroids and IVIg
D) Red cell exchange with C-negative RBC units

Answer: C

Rationale: The drop in hemoglobin to a lower level than the previous anemia after a transfusion supports the diagnosis of hyperhemolysis syndrome as a complication of a delayed hemolytic reaction with the formation of a new anti-C alloantibody. Transfusions (including red cell exchange) should be avoided unless anemia is life-threatening. First line therapy is immunosuppression with steroids and IVIg. Eculizumab is a second line agent for hyperhemolysis syndrome.

Iron Metabolism Disorders & Hemolytic Anemias : Livia Hegerova, MD

Question 1: A 31 yo woman G1P0 at 29 weeks gestation is referred for evaluation of anemia. At obstetrician visit hemoglobin 9, ferritin 10, iron saturation 10%. Which of the following is the most appropriate therapy?

A) Administration of EPO stimulating agents
B) Administration of iron sucrose
C) Administration of oral ferrous sulfate
D) Treatment with packed red blood cells

Question 2: A 19 yo man is evaluate for anemia after a recent urinary tract infection treated with trimethoprim/sulfamethoxazole. Laboratory evaluation showed Hgb 6.9 g/dL, retic 11%, negative Coombs, bilirubin 6. Which of the following is most likely cause of this patient's anemia?

A) PK deficiency
B) Hereditary spherocytosis
C) G6PD deficiency
D) B12 deficiency

Hematopoietic Cell Transplantation : Naveed Ali, MD

Question 1: A 55-year-old male with FLT3+ AML in complete remission following induction with 7+3 and midostaurin is being evaluated for allogeneic stem cell transplantation. He has 2 brothers. HLA typing reveals that both of his brothers are haploidentical match. An unrelated donor search reveals fully matched unrelated donors. In addition, he has 5/8 umbilical cord blood units available as well. A decision is made to proceed with a fully matched unrelated donor using peripheral blood stem cells. The patient inquires about using peripheral blood stem cells over bone marrow.

You tell him that:

A) Peripheral blood stem cells engraft faster than bone marrow
B) Bone marrow has higher incidence of chronic GVHD
C) Bone marrow has lower risks of graft rejection
D) Peripheral blood stem cells provide higher risk of relapse

Answer: A

Rationale: Peripheral blood stem cells engraft 5-7 days earlier than bone marrow. Bone marrow has a lower risk of chronic GVHD due to a smaller number of T-lymphocytes in the product relative to peripheral blood. Despite higher risk of chronic GVHD with peripheral blood stem cell transplant, peripheral blood grafts have almost replaced bone marrow as a stem cell source for treatment of hematological malignancies. This is because of lower relapse risk, more robust graft vs tumor effect and improvement in GVHD prevention strategies. Bone marrow is a preferred source when transplanting for non-malignant disorders where the goal of allogeneic transplant is restoration of hematopoietic system rather than graft vs tumor effect. Risk of graft rejection is higher with bone marrow transplant.

Question 2: A 45-year-old female with newly diagnosed AML with monosomy 7 who achieved complete remission following daunorubicin and cytarabine (3 + 7) induction. She then received high dose cytarabine consolidation prior to proceeding to a fully HLA matched sibling (brother) donor allogeneic transplant. Her conditioning regimen was myeloablative busulfan and cyclophosphamide. For graft vs host disease prophylaxis, she started on tacrolimus and received 4 doses of methotrexate on days 1, 3, 6 and 11. Currently, she is day 14 and has been complaining of right upper quadrant abdominal pain for the past 24 hours. She has not engrafted but her absolute neutrophil count is 0.3 x 106/µl. Her total bilirubin is 3.1 mg/dl. Liver enzymes are normal. Her serum creatinine is 1.7 mg/dl. Tacrolimus level is 8.2 ng/ml (therapeutic). Abdominal US showed normal gall bladder, liver measuring 14 cm and ascites. She had been taking ursodiol.

What is the next best management?

A) Start corticosteroids for acute liver GVHD
B) Start defibrotide for VOD
C) Start corticosteroids for engraftment syndrome
D) Closely observe, this is methotrexate induced liver toxicity and will resolve spontaneously
E) Reduce tacrolimus dose as this is tacrolimus induced nephrotoxicity

Answer: B

Rationale: She meets the criteria for diagnosis of VOD (onset within 21 days, hyperbilirubinemia, painful hepatomegaly and ascites). In addition, she has renal dysfunction in the setting of VOD. Treatment for VOD is indicated in her case. Early initiation of defibrotide reduces mortality. GVHD is unlikely prior to engraftment. Engraftment syndrome generally presents with fever, skin rash and evidence of fluid overload, and therefore unlikely to be the cause in her case. Methotrexate can cause liver dysfunction but her constellation of symptoms fit VOD. Tacrolimus level is therapeutic, so tacrolimus induced nephrotoxicity is less likely. Moreover, hyperbilirubinemia would not be explained by tacrolimus.

Question 3: A 27-year-old male is 42 days status post HLA matched unrelated donor peripheral blood stem cell transplant for high-risk B-ALL. His conditioning regimen was cyclophosphamide and 12 Gy TBI. His graft vs host disease prophylaxis was tacrolimus and methotrexate. He achieved neutrophil engraftment and largely recovered from gastrointestinal regimen related toxicities. He now presents to the clinic with 2-day history of new onset large volume diarrhea 7-8 times per day. He is admitted to the hospital where infectious workup is negative. A flexible sigmoidoscopy is performed which shows moderate to severe GVHD of the colon with many apoptotic cells and cryptic abscess. His stool volume is recorded at 1700 ml in 24 hours. He does not report nausea, vomiting or poor appetite. He does not have any skin rash and liver function is normal.

What would be the next step in management of his acute GVHD?

A) Start 0.5 mg/kg/day methylprednisolone
B) Start ruxolitinib 10 mg twice daily
C) Start 2 mg/kg/day methylprednisolone
D) Start budesonide and hold systemic corticosteroids for now
E) Start loperamide

Answer: C

Rationale: He has grade III acute GVHD of the lower GI tract. The standard treatment for grade III acute GVHD is 2 mg/kg/day methylprednisolone. Lower methylprednisolone dose (0.5-1 mg/kg/day) is used for grade I and II acute GVHD. Ruxolitinib was proven to be effective in REACH2 clinical trial as a treatment for steroid refractory acute GVHD and is FDA approved for this indication. Ruxolitinib would not be indicted for frontline therapy for acute GVHD. Budesonide is usually added to systemic steroids not as standalone treatment for grade III acute GVHD. Loperamide will not treat GVHD.

Transfusion Medicine : Rida Hasan, MD

Question 1: Which of the following is a rationale for needing a new type and screen sample every 3 days for hospitalized patients?

A) To decrease the risk of wrong blood in tube errors
B) To detect formation of new alloantibodies
C) To determine changes in blood type after bone marrow transplant
D) To increase detection of HLA antibodies
E) To detect presence of new autoantibodies

Answer: B.

Rationale: The reason for repeat type and screen samples every 3 days is to allow for detection of new alloantibodies against minor red cell antigens. A negative current screen will allow the patient to be eligible for an electronic crossmatch. If the antibody screen is positive, then a serologic crossmatch is needed and the serologic sample for the testing must be from the current type and screen.

Answer A is wrong because wrong blood in tube errors lead to wrong ABO types and acute hemolytic transfusion reactions. These errors are extremely rare. A 2 sample requirement (Type and screen and ABO confirmatory) on first time patients and a 2 person verification for each sample collected for T&S are used to decrease rates of wrong blood in tube errors. A patient's blood type is not expected to change with repeated type and screen outside of rare situations such as an ABO mismatched bone marrow transplant (C). While these changes could be picked up on a repeat blood type, it is not the rationale for this requirement. Answer D is incorrect because detection of HLA antibodies requires specialized testing. This testing is not routinely indicated unless there are concern for platelet refractoriness. Red cell autoantibodies are detected using a direct antiglobulin test (DAT).

Question 2: Which of the following is a part of the standard transfusion reaction workup?

A) Remove the IV from the site of the transfusion
B) Retain the remainder of the unit at patient's bedside
C) Repeat antibody screen
D) Pre-Transfusion sample hemolysis check
E) Post-Transfusion sample direct antiglobulin test

Answer: E.

Rationale: When a transfusion reaction is suspected, the clinical team should immediately stop the transfusion, notify the clinical team, evaluate the patient, notify the blood bank, and send both the remainder of the unit with the tubing and a post-transfusion sample to the blood bank. The test performed by the blood bank includes a repeat clerical check, repeat ABO type (not screen) and evaluation for hemolysis with a hemolysis check and a direct antiglobulin test on the post-transfusion sample (answer choice E). A positive DAT on a post-transfusion sample would indicate an immune mediated cause for the transfusion reaction such an acute hemolytic or delayed hemolytic transfusion reaction.

Answer A is incorrect because the IV site should be kept open with IV fluids infusing to allow for any acute interventions that may be needed if patient becomes unstable.

Answer B is incorrect because the remainder of the unit should be returned to the blood bank. Even if the workup is negative, the same unit should not be transfused to the patient. The only exception to this is a mild allergic reaction where the remainder of the unit may be transfused if the symptoms have completely resolved.

Answer C is incorrect because an ABO type is repeated to detect wrong blood in tube errors where the patient's sample may have been mislabeled. Only the ABO type is repeated, not the antibody screen.

Answer D is incorrect because the hemolysis check is routinely performed on the post-transfusion sample (not pretransfusion). If the hemolysis check is positive on the post-transfusion sample, then the medical director of the blood bank may decide to also perform a hemolysis check on the pre-transfusion sample to determine if the hemolysis is new since the transfusion occurred.

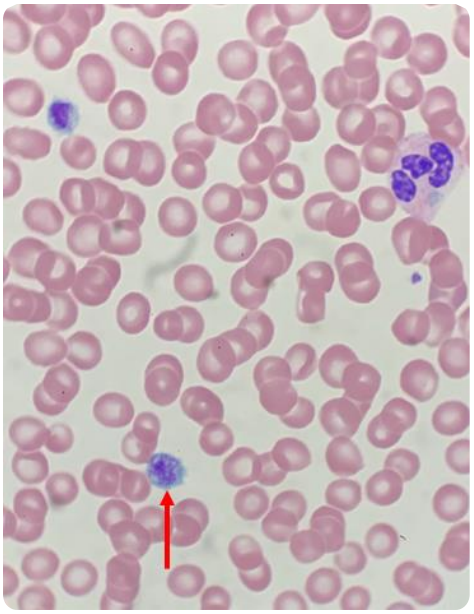
Thrombocytopenia : Sandhya Panch, MD, MPH

Question 1: A 28 yo female presents to hematology clinic. She has a family history of easy bleeding/ bruising in her father and brother. She has a personal history of frequent and prolonged episodes of epistaxis and heavy menstrual periods. Patient is also noted to have a family history of hearing loss. Previous steroid treatment failed to demonstrate response.

- Labs
- Mild microcytic anemia
- Iron deficiency
- Significantly decreased platelets (15-40X109/L)
- Peripheral smear : Large platelets and inclusion bodies in WBCs

What is the most likely diagnosis?

A) Bernard Soulier Syndrome
B) Glanzman's thrombasthenia
C) MYH9-related thrombocytopenia
D) Immune thrombocytopenia (ITP)



Answer: C

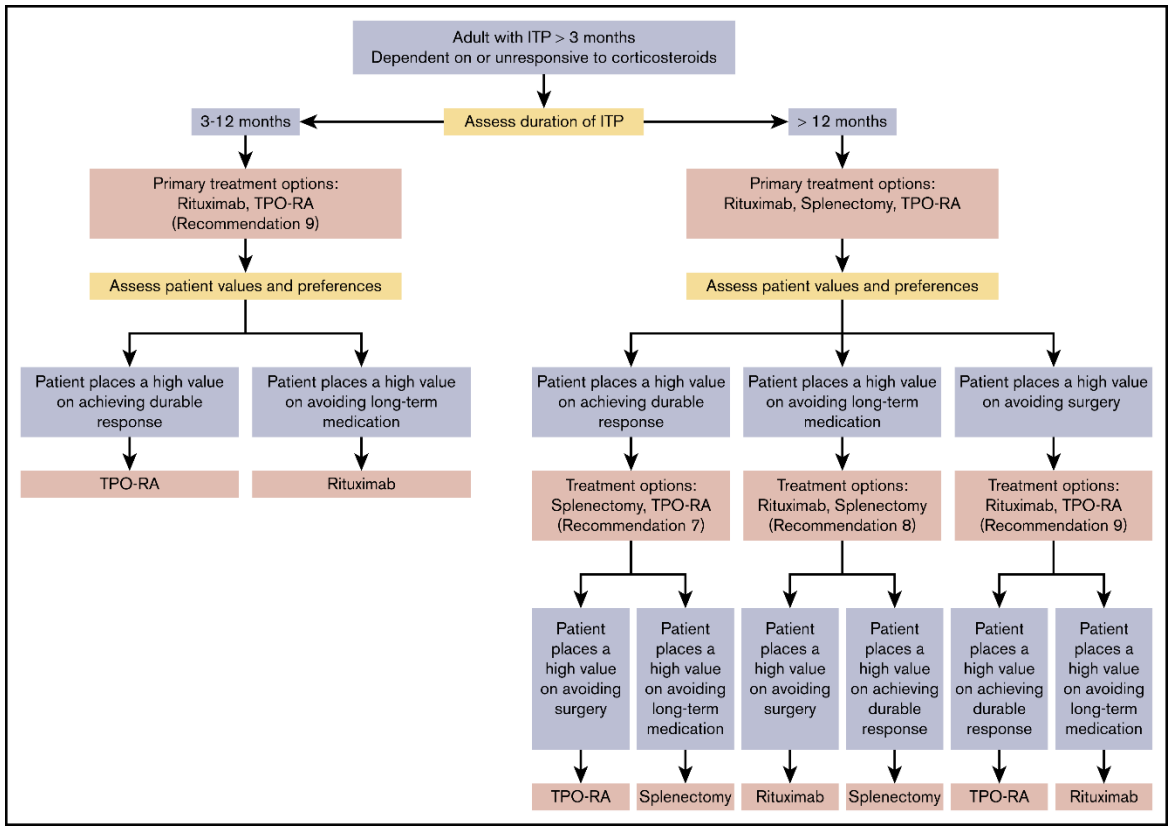
Rationale: Personal and family history suggest an inherited bleeding disorder ruling out ITP. Failure to steroids also points against an acquired autoimmune condition like ITP. Inclusion bodies in the WBCs, large platelets in low numbers and hearing loss are characteristic of a syndromic macrothrombocytopenia, specifically myosin heavy chain-9 related thrombocytopenia

Question 2: 42yo female with Immune thrombocytopenia (ITP) diagnosed 1 year ago (platelet nadir 3X109/L) and responded to a short course of steroids (120X109/L) now presents with platelet counts of 40X109/L. Counts repeated within a week are still at 40X109/L. She reports no bleeding/bruising. What are her management options?

A) Initiate TPO-RA
B) Re dose prednisone +/- IVIG
C) Initiate rituximab
D) Observe
E) Refer for splenectomy

Answer: D

Rationale: The 2019 American Society of Hematology guidelines for ITP management do not recommend treating patients with counts >30X109/L unless they are symptomatic (i.e. have bleeding or other sequelae). Patient reports no bleeding or bruising symptoms. It would hence be reasonable to monitor her closely with serial CBCs.



Question 3: 32 yo female presents 1 week post partum with fatigue and headaches. BP is elevated at 178/106 HR: 120/min. O2 sats: 98%.
Labs

- WBC: 5500/mm3
- Hb: 11gm/dl→7.5gm/dL; schistocytes +++
- Platelets: 130 X109/L→35 X109/L
- PT/aPTT normal; Fibrinogen: 300mg/dL; AST/ALT: Normal; LDH: 850U/L; Creatinine 0.8mg/dL→4.8mg/dL

What is the most likely diagnosis?

A) Disseminated Intravascular Coagulation (DIC)
B) Hemolysis, Elevated Liver Enzymes, Low Platelets (HELLP) syndrome
C) Thrombotic Thrombocytopenic Purpura (TTP)
D) Atypical Hemolytic Uremic Syndrome (aHUS)

Answer: D

Rationale: Elevated blood pressure, microangiopathic hemolytic anemia, new onset thrombocytopenia, normal coagulation profile and normal transaminases, but with significant creatinine elevation suggests aHUS

	Preeclampsia/HELLP	TTP	HUS	AFLP
Elevated blood pressure	+++	+	+	++ (50% of cases)
Neurological symptoms	+/++ (headache)	+++ (numbness, weakness, aphasia, mental status)	+	+
Abdominal symptoms	+ (RUQ pain)	++ (unspecific/diffuse)	+	+++ (unspecific/diffuse)
Fever	–	–/+	–/+	–
Easy bruising	–	–/+	–	–
Thrombocytopenia	+/++ (>50 × 10^9/L)	+++ (<20 × 10^9/L)	+ (<100 × 10^9/L)	+
Renal impairment (elevated creatinine; > ~2 mg/dL)	+/++	+/++	+++	++/+++
Hepatic dysfunction and inflammation (AST/ALT)	+	–/+	–/+	+++ (and bilirubin)
Coagulopathy	–/+	–	–	+++
LDH	+	+/+++	+/++	+++
Microangiopathic hemolytic anemia	+	+/+++	+/++	+
Hypoglycemia	–	–	–	+
ADAMTS13 activity	Normal	<10%*	>20%-30%†	>30%

Bleeding Disorders : Allison P Wheeler, MD, MSc

Questions 1: A 25-year-old female presents for evaluation prior to tonsillectomy due to a history of heavy menstrual bleeding since menarche. During the history it is revealed that she experienced epistaxis as a child and easy bruising; she also notes that she experienced bleeding after her wisdom teeth were removed and had to have a second procedure with her dentist. Laboratory testing shows: normal PT and PTT, normal platelet count and decreased Von Willebrand factor antigen with a more significant decrease in Von Willebrand factor activity. What is the most appropriate treatment prior to her tonsillectomy scheduled next week?

A) Platelet transfusion
B) Von Willebrand factor concentrate
C) DDAVP
D) Fresh frozen plasma
E) Vitamin K

Answer: B) Von Willebrand factor concentrate.

Rationale: The patient's presentation is concerning for a functional defect in her Von Willebrand factor given the more significant decrease in her Von Willebrand factor activity compared to antigen. This concern makes Von Willebrand factor concentrate a superior choice to DDAVP, which would result in release of endogenous Von Willebrand factor and also requires a challenge test for efficacy. While platelets and plasma are both sources of Von Willebrand factor, the direct concentrate is superior to both. Vitamin K would result in correction of factors II, VII, IX and X in the setting of a vitamin K antagonist (e.g. warfarin).

Questions 2: Treatment for hemophilia has evolved significantly with a burst of innovation over the past decade. For a 21-year-old patient with hemophilia B who has a history of a factor IX inhibitor that was tolerized when he was 3 years old, what treatment option is NOT appropriate for his prophylaxis?

A) rIXFc
B) Concizumab
C) Fitusiran
D) Emicizumab
E) N9-GP

Answer: D) Emicizumab

Rationale: Emicizumab is a factor VIII mimetic and would only be used in patients with hemophilia A (with or without inhibitors), thus would not be appropriate for a patient with hemophilia B.

(1) rIXFc and (5) N9-GP are both extended half life products that would be appropriate in this patient. However, if his inhibitor had not been tolerized (aka he still had an active inhibitor) then these drugs would not be affective. (2) Concizumab, an anti-TFPI monoclonal antibody, and (3) Fitusiran, a small interfering RNA molecule that results in decreased antithrombin, both are sub-cutaneous options that provide prophylactic benefit for patients with hemophilia A or B with or without inhibitors.

Thrombosis & Anticoagulation : David A. Garcia, MD

Question 1: You are asked to provide peri-operative anticoagulation recommendations for a 74-year-old man with diabetes and hypertension who takes rivaroxaban daily for atrial fibrillation He will have a ventral hernia repair under general anesthesia; his renal function is normal. The surgical team plans to resume his rivaroxaban the day after the operation. Regarding pre-operative rivaroxaban, you advise that he:

A) Omit rivaroxaban doses 1-2 days before surgery.
B) Omit rivaroxaban dosses for 5 days prior to (and the day of) surgery without LMWH 'bridging'.
C) Omit rivaroxaban doses 1-2 days before surgery; measure stat anti-Xa level before surgery and proceed only if rivaroxaban level is undetectable.
D) Omit rivaroxaban dosses for 5 days prior to (and the day of) surgery with LMWH 'bridging'.

Answer: A

Rationale: Evidence from a large, controlled prospective cohort study demonstrates that, unless a patient has severe renal impairment, a 24-48 hour interruption (without bridging) is sufficient for a medication like rivaroxaban. [Douketis et al. JAMA Intern Med. 2019;179(11):1469-1478] Performing a hernia repair without interrupting rivaroxaban would result in an unacceptable bleeding risk.

Question 2: A 25-year-old woman with experiences pulmonary embolism and stops rivaroxaban therapy after 6 months of treatment. 8 months later, she is diagnosed with cerebral vein thrombosis. You are now seeing her about 6 months after the second VTE episode. Laboratory testing shows repeatedly and strongly positive tests for anticardiolipin and anti-beta-2 GP I antibodies. She also has at least one strongly positive lupus anticoagulant (performed before she started anticoagulants for a second time). What treatment would you recommend going forward?

A) Rivaroxaban 20 mg daily
B) Warfarin, target INR 2-3
C) Warfarin, target INR 3-4
D) Enoxaparin 1.5 mg/kg SC daily
E) Aspirin 81 mg daily

Answer: B

Rationale: a meta-analysis of 3 randomized controlled trials of patients with triple-positive anti phospholipid syndrome indicates that oral factor Xa inhibitors may be less effective than warfarin in preventing arterial thrombosis. [J Am Coll Cardiol. 2023;81:16–30] Aspirin monotherapy would likely be less effective than warfarin at preventing further (especially venous) thrombosis episodes. Long term enoxaparin wold be very burdensome and not well studied as an extended secondary prevention strategy for patients with thrombotic APS. For APS patients treated with warfarin, at least two randomized trials have shown that a target INR 2-3 is as effective as a higher target INR. [N Engl J Med. 2003 Sep 18;349(12):1133-8 and J Thromb Haemost. 2005 May;3(5):848-53}

Question 3: A 64-year-old man with atrial fibrillation, a prior history of ischemic stroke, and a history of unprovoked pulmonary embolism presents with a headache and found to have evidence of subarachnoid hemorrhage on CT scan. He is awake and alert with a Glasgow coma scale score of 15. He takes rivaroxaban 20 mg daily; his last dose was approximately 26 hours ago. His estimated GFR is > 60 ml/min.
The best recommendation, in addition to withholding further doses of rivaroxaban, is to:

A) Administer fixed-dose prothrombin complex concentrate (e.g. KCentra 2000 units IV)
B) Check a PT and PTT
C) Check a thrombin time
D) Administer andexanet alpha bolus plus continuous infusion.
E) Monitor closely for deterioration

Answer: E

Rationale: The patient's history puts him at significant risk for both arterial and venous thrombosis. Andexanet alpha can reverse the effects of rivaroxaban but will increase the risk of clotting (especially ischemic stroke). [Connolly et al N Engl J Med 2024;390:1745-1755] Since the last dose of rivaroxaban was > 24 hours ago, it is likely that little anticoagulant effect is present (this could be confirmed with an antiXa level; PT, PTT and thrombin time would be misleading and/or unhelpful). PCC is not appropriate here but may be helpful in situations where (a) urgent reversal of the FXa inhibitor is mandatory and (b) andexanet alpha is unavailable.

Consultative Hematology : Prakash Vishnu, MD, FACP

Question 1: A 44-year-old female presents with iron deficiency anemia that has not improved after 6 months of oral iron repletion.

What laboratory test result would best support a primary defect in heme biosynthesis?

A) Positive h.pylori stool antigen
B) Ringed sideroblasts in bone marrow
C) Hemochromatosis HFE gene mutation
D) Increased hemoglobin A2

Answer: B

Rationale: Ringed sideroblasts detected by Prussian blue stain on bone marrow specimens reflect the presence of iron laden mitochondria encircling the erythroid nucleus. Ringed sideroblasts may be seen in association with hereditary or acquired defects in heme biosynthesis. Answer choice A is incorrect. A positive stool antigen test for h.pylori would support an impairment in iron absorption. Answer choice C is not correct since HFE gene mutations are associated with iron overload. Answer choice D is not correct because increased Hgb A2 is associated with beta thalassemia, which would impair beta globin synthesis.

Question 2: A 65-year-old male presents with polycythemia, with a hematocrit of 58%. What test result would best support a diagnosis of compensatory polycythemia?

A) JAK2V617F DNA mutation
B) Decreased serum erythropoietin
C) Decreased hemoglobin P50
D) Hepatic mass on CT imaging

Answer: C

Rationale: A decreased hemoglobin P50 reflects a shift of the hemoglobin oxygen dissociation curve to the left. This can be seen in the setting of chronic carbon monoxide exposure due to cigarette smoking and impaired oxygen delivery to tissues, resulting in compensatory polycythemia. Answer choices A and B are not correct. JAK2V617F DNA mutation and decreased serum erythropoietin would both support a diagnosis of primary polycythemia vera. Answer choice D is not correct. A hepatic mass on CT imaging could support the presence of an epo-secreting tumor.

Question 3: Which of the following is a feature in a patient with acquired porphyria cutanea tarda (PCT) ?

A. Responsiveness to vitamin B6
B. Defect in ferrochelatase activity
C. Buildup of metal free protoporphyrin
D. Iron dependent UROD inhibition

Answer: D

Rationale: Iron-dependent inhibition of UROD is a feature of acquired PCT. In acquired (sporadic) PCT, hepatic iron overload and oxidative stress lead to the formation of an inhibitor of UROD, specifically uroporphomethene, which is generated by iron-dependent oxidation of uroporphyrinogen. This inhibitor competitively impairs UROD activity, resulting in the characteristic accumulation of uroporphyrins. Answer choices A, B and C are not correct. Defect in ferrochelatase activity, build-up of metal free protoporphyrin and responsiveness to vitamin B6 are all seen in erythropoietic porphyria.