Fred Hutch Cancer Center

15th Annual Hematology Oncology Review Course

Question & Answer

UW Medicine

Table of Contents

Day **Page**

Monday, September 23

Anal Cancer : Andrew Coveler, MD

Question 1: A 48-year old woman presents with rectal bleeding and pain and 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) Chemoradiotherapy using 5-FU or Capecitabine and Mitomycin C
B) Abdominoperineal resection
C) Endoscopic ultrasound and transanal excision
D) Induction chemotherapy with 5-FU and cisplatin followed by definitive chemoradiotherapy

Answer: A

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.

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-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: The correctly matched molecular alteration and its associated approved targeted therapy(s) for metastatic colorectal cancer is:

A) BRAF / encorafenib with cetuximab
B) EGFR / erlotinib
C) HER2 / trastuzumab
D) NRAS / cetuximab or panitumumab

Answer: A

Rationale: Biomarkers are helpful in selecting which targeted therapy agents may be beneficial or harmful for a particular patient. The BEACON trial established encorafenib and cetuximab as a standard for metastatic colorectal cancers with BRAF V600 mutations (A). Mutations in KRAS and NRAS, predict lack of benefit from anti-EGFR therapy, such as cetuximab or panitumumab (D). Unlike lung cancer, alterations in

EGFR fail to predict benefit from erlotinib and other EGFR-directed TKIs and these agents are not used (B). While HER2 suggests benefit from HER2-directed therapy, trastuzumab should be given in a doublet with a second targeted agent, such as tucatinib. Thus, trastuzumab monotherapy is not recommended (C).

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.

Question 2:

- 62 yo engineer, healthy, presents with epigastric discomfort radiating to the left side.
- Multiphase CT abdomen and pelvis shows a pancreatic body mass encasing the celiac artery and abutting the SMA as well as the SMV.
- CT chest shows no distant metastases.
- CA 19-9 = 63
- ECOG performance status 0

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

Rationale:

- Surgical resection offers the only chance of cure for nonmetastatic pancreatic cancer.
- This patient has locally advanced, unresectable disease due to local vascular invasion.
- An initial period of chemotherapy is recommended (rather than radiotherapy or chemoradiotherapy).
- If aggressive medical therapy permits, combination chemotherapy with mFOLFIRINOX is preferred.
- Resectability should be assessed after 4-6 months of neoadjuvant therapy.
- Chemoradiation may be considered to optimize local control in those patients who can no longer tolerate further chemotherapy but who continue to have localized disease, unresectable and maintain a good performance status

Question 3:

- 55 year-old woman presents for a 2nd-opinion.
- Diagnosed with a tail of pancreas mass with bilateral lung metastases and extensive intra-abdominal lymphadenopathy.
- CA 19-9 = 94,592
- Tumor next generation sequencing: BRAF V600E mutation, microsatellite stable
- ECOG performance status 1
- Received 1st-line mFOLFIRINOX with good tolerability.
- Stable disease, CA 19-9 nadir 36,814.
- Then disease progression after 6 months.

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:

E) Observation
F) Capecitabine adjuvant therapy
G) Gemcitabine and cisplatin adjuvant therapy
H) 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: A

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 v1.2025
- 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 v1.2025

Prostate Cancer : Michael Schweizer, MD
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) Rucaparib
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.

Rucaparib is approved in men with mutations in either BRCA1/2 who have progressed on both a novel hormonal agent and docetaxel. 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) Darolutamide

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 : Jessica Hawley, MD, MS

Question 1: A 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.

What do you do next?

A) Begin intra-vesical therapy with BCG
B) Schedule a cystoprostatectomy with lymph node dissection.
C) Begin systemic chemotherapy with cisplatin-based chemotherapy w/ ddMVAC or GC.
D) Start pembrolizumab.

Answer: C

Rationale:

- Cisplatin-based chemotherapy is the standard of care treatment for muscle-invasive urothelial carcinoma (T2-4).
- BCG and pembrolizumab are used in NMIBC.
- SWOG Intergroup Trial established role for NAC before RC. 5-yr survival for surgery alone 43% vs. NAC + RC 57%
- VESPER trial showed ddMVAC is better than GC but both are reasonable depending on patient comorbidities, age.
- 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 the only currently FDA-approved therapy in this setting, although we await decision from FDA about adjuvant pembrolizumab. Erdafitinib is approved in the 2nd line setting of for patients w/ FGFR3 activating mutations in the locally adv / metastatic setting. 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.

Question 3: Which is the most common adverse events of enfortumab vedotin:

A) Skin reactions
B) Peripheral neuropathy
C) Hyperglycemia
D) All

Answer: D

Rationale: All of these side effects are seen w/ EV, owing to the MMAE (antimitotic agent) payload. Patients who are candidates to receive enfortumab vedotin should receive a complete skin examination, ophthalmological assessment, measurement of glucose levels and kidney function, and a neurological evaluation. Patients with uncontrolled diabetes mellitus (HbA1c ≥8 percent or HbA1c 7 percent to <8 percent with associated symptoms of diabetes), a severe dermatologic condition, grade ≥2 neuropathy, and/or creatinine clearance ≤30 mL/minute are ineligible for this regimen.

Tuesday, September 24

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)

References

Garon et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment for stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicenter, double-blind, randomized phase 3 trial. Lancet 2014;384(9944):665-73

Garon et al. Pembrolizumab for the treatment of non-small cell lung cancer. NEJM 2015;372:2018-28

Lisberg et al. A Phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naïve patients with advanced NSCLC. JTO 2018. https://doi.org/10.1016/j.jtho.2018.03.035

Paz-Ares et al. Pembrolizumab plus chemotherapy for squamous non-small cell lung cancer. NEJM 2018;379:2040

Reck et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small cell lung cancer. NEJM 2016;375:1823-1833

Sandler et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. NEJM 2006;355:2542-50

Soria et al. Osimertinib in untreated EGFR-mutated advanced non-small cell lung cancer. NEJM 2018; 378(2):113-125

Scagliotti et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced stage non-small cell lung cancer. J Clin Oncol 2008;26(21):3543-3551

Schoenfeld et al. Severe immune-related adverse events are common with sequential PD-(L1)1 blockade and osimertinib. Ann Oncol 2019; 30: 839-844

Small Cell Lung Cancer : Nicholas P. Giustini, 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 for patients with tumors <7 cm and clinically node negative in order to ensure resectability.
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 discussed and 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 done for tumors <5 cm and clinically node negative to evaluate for resectability. Answer (C) is incorrect because resection is considered for T1-2 (tumor <5 cm) N0 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 treatment option, EXCEPT:

A) Lurbinectedin
B) Topotecan
C) Tarlatamab
D) Carboplatin/etoposide

Answer: D

Rationale: Carboplatin/etoposide rechallenge is not recommended because the patient has experienced disease progression <3 months from prior carboplatin/etoposide exposure (answer D). Lurbinectedin (answer A), topotecan (answer B), or tarlatamab (C) would all be acceptable second line treatment options with a preference for tarlatamab given recently published data showing impressive overall survival in the recurrent setting.

Mesothelioma : Nicholas P. Giustini, MD

Question 1: A 70 year-old male with a history of HTN, COPD, afib c/b thromboembolic CVA 3 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
D) Ipilimumab/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 reasonable.

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) Ipilimumab/nivolumab is the preferred first line treatment choice for 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 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). Ipilimumab/nivolumab is the preferred treatment choice for unresectable non-epithelioid (biphasic or sarcomatoid) mesothelioma (answer B). Robust data do not exist showing EPP or P/D as a superior surgical approach (answer D).

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.

e) 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 ✍ 2 cm and 1.2 ✍ 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 trilas (including NADINA) have revived the role of combination ICI in earlier stages of melanoma.

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 abema discontinuation

Question 6: 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.

Which of the following statements are true about laboratory abnormalities associated with CDK 4/6 inhibitors?

A) Abemaciclib may cause a false elevation in serum creatinine.
B) Abemaciclib and ribociclib may cause a false elevation in serum creatinine.
C) The incidence of neutropenia is similar across abemaciclib, ribociclib, and palbociclib.
D) Abemaciclib is associated with transaminitis.

Answer: A

Question 7: BB is a 79 year old man with a new diagnosis of right upper tract urothelial carcinoma with metastases to the L acetabulum. He will be initiating therapy with enfortumab vedotin and pembrolizumab along with zoledronic acid to reduce the risk for bone fractures.
Two weeks after initiation, patient's non-fasting blood glucose was 268mg/dl. His last random blood glucose was 87mg/dl with no history of diabetes or hyperglycemia. Which statement best represents the next course of action?

A) Hold pembrolizumab and enfortumab vedotin
B) Continue pembrolizumab and hold enfortumab vedotin
C) Hold pembrolizumab and continue enfortumab vedotin
D) Continue both pembrolizumab and enfortumab vedotin

Answer: B

Rationale: Although A is reasonable if we want more time to evaluate, as well as we would expect irreversible damage from pembro and reversible from enfortumab
Both can lead to blood glucose changes so we have to look at timing, reversibility

Question 8: SR is a 55 year old man with adenocarcinoma of the sigmoid colon with metastases to the liver. The molecular profile reveals an ERBB2 copy number gain, MSS, and TMB 5.3 mutations/mb. He has received FOLFOX with bevacizumab, CapeOx, and FOLFIRI in the past. He last received FOLFIRI 2 months ago with progression on this regimen. He has residual debilitating neuropathy from oxaliplatin. SR will be starting tucatinib + trastuzumab.

SR reports feeling nervous about the adverse effect profile of the capecitabine he received in the past and the tucatinib, based on the patient education handouts he has read. Which of the following are reported overlapping adverse effects of capecitabine and tucatinib?

A) Cardiotoxicity
B) Hand-foot syndrome
C) Diarrhea
D) Transaminitis
E) All of the above

Answer: E

Question 9: BT is a 62 year old women with metastatic EGFR L858R adenocarcinoma of the right lung with metastases to the ribs, sacrum, and brain. She was on osimertinib for the past 8 months. She develop osimertinib related pneumonitis and stopped osimertinib. Her most recent imaging shows a new concern for leptomeningeal disease. She will be starting amivantamab and lazertinib.

A) What supportive care should be recommended for BT (select all that apply)?
B) Apixaban 2.5mg BID for four months
C) Enoxaparin 1mg/kg daily for four months
D) Oral doxycycline 100mg BID
E) Topical emollient creams and limiting sun exposure

Answer: A, C and D

Question 10: ML tolerates Cycle 1 of chemotherapy well. She presents for Cycle 2 and receives pembrolizumab, bevacizumab, and paclitaxel. Right as her infusion of cisplatin starts, she has low back pain, flushing, and itching. It resolved with diphenhydramine. Which of the following statements best represents hypersensitivity reactions with this regimen?

A) This is likely a paclitaxel reaction. Continue premedications and consider increasing diphenhydramine dose or a rate titration with next infusion.

B) This is likely a cisplatin reaction. Reactions to platinum compounds are most common with cisplatin in the 1st or 2nd infusion.
C) As she's received pembrolizumab, bevacizumab, and paclitaxel, it could be either of the three agents. Rate titrate all three agents for subsequent infusions.
D) This is likely a cisplatin reaction. She will require cisplatin desensitization for future cycles.

Answer: A

Rationale: Paclitaxel reactions are most likely to occur during the first or second infusion and are due to the cremaphor diluent.
-Taxane hypersensitivity reactions can be managed with slowing the rate of infusion and additional premedications.
-Of the platinum compounds, reactions are most common with carboplatin and this is most common during cycles 6 – 8 of carboplatin. These can be managed with desensitization with future cycles.
-Infusion reactions are rare with pembrolizumab and bevacizumab.

Question 11: ML is a 60 year old woman with adenocarcinoma of the cervix extending to the uterus and upper vagina with abutment of the rectosigmoid junction. Her PET scan showed avid right external iliac nodal metastasis as well as hypermetabolic nodules in the lung. She initiated cisplatin + paclitaxel + bevacizumab + pembrolizumab.

ML arrives for Cycle 3 of this regimen. Her blood pressure in clinic is 165/90 and she does not know what her home blood pressure is. She is not on any anti-hypertensives. Her BP prior to starting chemotherapy was 130s/80s. Which of the following is an appropriate strategy to manage bevacizumab induced hypertension?

A) Start amlodipine 5mg daily. Hold bevacizumab infusion today
B) Start lisinopril 10mg. Hold bevacizumab infusion today.
C) Continue bevacizumab infusion, start amlodipine 5mg daily.
D) Continue bevacizumab infusion, have patient start monitoring home blood pressure.

Answer: A, B, C and D

Rationale: All the above can be options. Consider:
-Availability of at-home blood pressure monitoring
-Concomitant nephrotoxicity with cisplatin
-Concerns with medication adherence
-Disease control

Question 12: ML is a 60 year old woman with adenocarcinoma of the cervix extending to the uterus and upper vagina with abutment of the rectosigmoid junction. Her PET

scan showed avid right external iliac nodal metastasis as well as hypermetabolic nodules in the lung. She initiated cisplatin + paclitaxel + bevacizumab + pembrolizumab.

Which of the following are guideline-based recommendations for treatment or prevention of chemotherapy induced peripheral neuropathy? (Select all that apply)

A) There are no pharmacologic agents recommended for the prevention of CIPN
B) Duloxetine may be recommended for treatment of CIPN, starting at 30mg daily for a week, then 60mg daily.
C) Cryotherapy to the hands and feet may be considered to decrease the risk for neuropathy
D) Vitamin B12, glutamine, and folic acid may be used to decrease the risk for neuropathy.

Answer: A, B and C

Rationale: Cumulative dose effect with platinums and taxanes
-Primary sensory neuropathy with stocking-glove distribution with taxanes (primarily paclitaxel) and platinums (primarily oxaliplatin and cisplatin).
-Paclitaxel neuropathy tends to improve over months after cessation of therapy
-Oxaliplatin neuropathy tends to worsen over 2-3 months after cessation of therapy, then improves.

Question 13: AK is a 66 year old woman with Stage IIIC2 high grade uterine carcinoma. She has received neoadjuvant carboplatin + paclitaxel one year ago, followed by debulking surgery with pathology revealing p53 overexpression, HER2 1+ by IHC, FOLR1 30% by IHC (negative), and MSS and TMB-L. She started pembrolizumab + levnatinib with progression after 7 cycles. She is now starting trastuzumab deruxtecan.

After 4 cycles, AK reports new shortness of breath and cough. Imaging reveals pneumonitis. Which of the following statements best represents management of trastuzumab deruxtecan related ILD?

A) Hold trastuzumab deruxtecan, initiate prednisone 1mg/kg until symptom resolution, then taper. Rechallenge with trastuzumab deruxtecan is contraindicated.
B) Continue trastuzumab deruxtecan, initiate prednisone 1mg/kg until symptom resolution, then taper. Rechallenge with trastuzumab deruxtecan is contraindicated.
C) Hold trastuzumab deruxtecan, initiate prednisone 1mg/kg until symptom resolution, then taper. Consider rechallenge with shared, multidisciplinary decision making.

D) Continue trastuzumab deruxtecan, initiate prednisone 1mg/kg until symptom resolution, then taper. Rechallenge with trastuzumab deruxtecan is contraindicated.

Answer: A and C

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.

Metastatic Breast Cancer : Natasha B. Hunter, 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) AC followed by paclitaxel
B) TAC (docetaxel, Adriamycin, and cyclophosphamide)
C) Carboplatin and gemcitabine
D) CMF (cyclophosphamide, methotrexate, and 5-FU)

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

Wednesday, September 25

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 : Renata R. Urban, MD

Question 1: A 75 year-old obese female undergoes endometrial biopsy for postmenopausal bleeding which demonstrates grade 3 endometrioid adenocarcinoma. She undergoes surgical staging which reveals carcinoma in a paraaortic lymph node. . What treatment option would NOT be appropriate?

A) Carboplatin, paclitaxel & dostarlimab
B) Carboplatin, paclitaxel & pembrolizumab
C) Carboplatin & paclitaxel, followed by radiation
D) Whole abdominal radiation
E) Pelvic radiation, followed by carboplatin & paclitaxel

Answer: D

Rationale: All are reasonable treatment options with the exception of whole abdominal radiation (WAR). Historically, whole abdominal radiation (WAR) was considered the standard of care for advanced endometrial cancer. However, chemotherapy was found to have improved outcomes and reduced toxicity compared to WAR in the GOG 122 trial; the subsequent GOG 209 trial showed that carboplatin and paclitaxel were not inferior to the TAP regimen. GOG 258 compared carboplatin and paclitaxel to chemoradiation followed by carboplatin and paclitaxel. Both treatment arms had similar progression-free and overall survival.

Most recently, three phase III trials demonstrated the superiority of chemotherapy with checkpoint blockade. The GY019 and RUBY trials showed improved PFS and OS with the addition of pembrolizumab and dostarlimab; greater benefit was seen in patients with dMMR/MSI-H tumors.

References

Randall ME et al. J Clin Oncol 2006.

Miller DS et al. Gynecol Oncol 2012.
Matei D et al. New Engl J Med 2018
De Boer SM et al. Lancet Oncol 2019.
Eskander RN et al. N Engl J Med 2023.
Mirza MR et al. N Engl J Med 2023.

Question 2: A 65 year-old woman was treated with cisplatin plus radiation for stage III squamous cell carcinoma of the cervix 3 years ago. She has developed cough and mild dyspnea on exertion, and a chest x-ray showed multiple bilateral lung lesions. A biopsy of one lung lesion showed squamous cell carcinoma consistent with metastatic disease. PD-L1 imaging is performed and confirms CPS score of 10. CT imaging confirmed the multiple lung metastases as well as liver metastases. What is your management recommendation?

A) Treatment with weekly paclitaxel
B) Treatment with cisplatin and paclitaxel
C) Treatment with carboplatin, paclitaxel, pembrolizumab, bevacizumab
D) Treatment with tisotumab-vedotin

Answer: C

Rationale: GOG 240 showed that the addition of bevacizumab to chemotherapy improved overall survival for advanced/recurrent cervical cancer in a randomized phase 3 trial. In this 2x2 factorial design, two chemotherapy arms were included– cisplatin and paclitaxel vs. topotecan and paclitaxel. Topotecan and paclitaxel was not superior to cisplatin and paclitaxel, even in patients who had received prior cisplatin. Addition of bevacizumab to either chemotherapy arm improved survival, with an overall survival of 17 months versus 13.3 months. JCOG 0505 was a randomized phase III trial of cisplatin and paclitaxel versus carboplatin and paclitaxel. Carboplatin and paclitaxel was not inferior to cisplatin and paclitaxel for overall survival. However, it is important to note that for patients who had not previously cisplatin (for chemosensitization with RT, or as primary chemotherapy), cisplatin and paclitaxel was superior to carboplatin and paclitaxel. For this patient, since she received cisplatin with initial radiation, substitution of carboplatin for cisplatin would be preferred, given similar survival and better side effect profile.

Pembrolizumab has been approved in combination with chemotherapy with or without bevacizumab for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1, and would be considered first-line therapy for metastatic cervical cancer.

Tisotumab-vedotin (TV) is an antibody-drug conjugate approved for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. In a phase III trial, TV was associated with improved profession-free and overall survival compared to investigator's choice chemotherapy. However, given that the patient has

not received chemotherapy for her metastatic disease, this would not be the first-line therapy.

References:

Kitagawa R et al. J Clin Oncol 2015.
Colombo N et al. N Engl J Med 2021.
Coleman RL et al. N ENgl J Med 2024.

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

Familial Syndromes : Marshall Horwitz, 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: 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: Two individuals of Ashkenazi Jewish ancestry have a child together. In which situation will their offspring be at risk for the onset of cancer during childhood?

A) One parent carries (i.e. is heterozygous for) the BRCA1 185delAG mutation and the other parent carries the BRCA1 5382insC mutation.
B) One parent carries (i.e. is heterozygous for) the BRCA1 185delAG mutation and the other parent carries the BRCA2 6174delT mutation.
C) One parent carries (i.e. is heterozygous for) the BRCA1 185delAG mutation and the other parent is heterozygous for the MSH2 A636 mutation.
D) One parent carries (i.e. is heterozygous for) the BRCA1 185delAG mutation and the other parent lacks a mutation in known cancer predisposition genes.

Answer: There are three "founder" mutations responsible for hereditary breast ovarian cancer syndrome prevalent in the Ashkenazi Jewish population (BRCA1 185delAG, BRCA1 5382insC, BRCA2 6174delT). Similarly, there are founder mutations for Lynch syndrome occurring in the Ashkenazi Jewish population, including MSH2 A636P. BRCA1 and BRCA2, along with a score or so of other genes, encode components of the Fanconi DNA repair complex. Homozygosity for any one of those genes (i.e. germline mutations occurring on both the maternal and paternal allele for BRCA1) cause Fanconi anemia; compound heterozygosity (i.e. germline mutations occurring on the maternal allele for BRCA1 and paternal allele for BRCA2) do not. A similar situation holds for Lynch syndrome: when a person is biallelic for mutations in a gene responsible for Lynch syndrome, they will manifest constitutional mismatch repair-deficiency syndrome, which also leads to childhood cancer predisposition. For the correct answer (A), each of the couple's conceptions will have a risk of 1/4 for inheriting Fanconi

anemia, a risk of 1/2 for inheriting hereditary breast ovarian cancer syndrome, and a probability of 1/4 of not inheriting neither hereditary breast ovarian cancer syndrome or Fanconi anemia. The reason why individuals who inherit biallelic germline mutations in tumor suppressor genes develop cancer during childhood is because no second hit is required to initiate tumorigenesis.

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] : Jonathan Chen, MD, PhD

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

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

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

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

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 resultant edema of the left leg that is uncomfortable. LDH is wnl, repeat biopsy shows classic FL, and molecular testing of the biopsy reveals EZH2 WT. 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, noting efficacy in EZH2 WT as well as EZH2 mutated FL
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% 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 a significant 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 has an incisional biopsy of an enlarged cervical LN. This shows architectural effacement by a follicular pattern of B-lymphocytes and 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.

T-Cell Lymphoma - NHL : Christina Poh, MD

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

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

Hodgkin Lymphoma : Christina Poh, 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, September 26

Infectious Disease Complications : Danniel Zamora, MD

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: How soon after initiating voriconazole therapy should you check a trough level?

Answer: 5-7 days

Rationale: Voriconazole has numerous drug-drug interactions with other medications commonly used in oncology which could increase or lower levels from therapeutic range. In addition, a subset of patients have genotypic variability in drug metabolism which could cause them to metabolize voriconazole differently.

Question 3: What is the definition of refractory CMV infection after hematopoietic cell transplantation?

Answer: CMV viremia that increases (i.e., >1 log10) OR persists (≤1 log10 increase or decrease) after at least 2 weeks of appropriate antiviral therapy.

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:

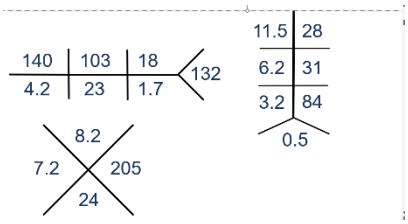
- Weight: 96 kg
- Blood pressure: 124/76

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:

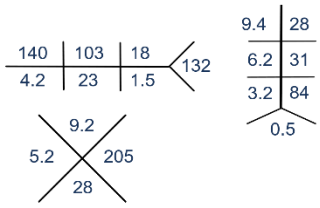
- Acyclovir 400 mg PO BID
- Apixaban 5 mg PO BID
- Metformin 1000 mg PO BID
- Metoprolol 50 mg PO BID
- Lisinopril 40 mg PO daily
- Atorvastatin 20 mg PO daily
- Gabapentin 600 mg PO TID
- Oxycodone 5 mg PO Q6H PRN pain

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:

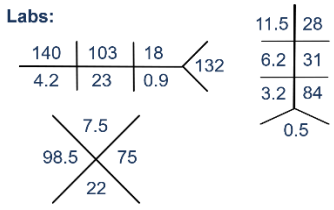
- History of breast cancer treated with lumpectomy and 4 cycles of doxorubicin/cytarabine followed by weekly paclitaxel x 12 doses. Completed about 2 years ago.

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 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.

A) Which one of the following treatment options is recommended?
B) Start single agent acalabrutinib or zanubrutinib and continue until progression

C) Start treatment with Pirtobrutinib and continue until progression
D) Start combination venetoclax and rituximab and continue for 2 years
E) All 3 options are reasonable.

Answer: D

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) Start venetoclax
C) Switch to second generation BTKi, zanubrutinib
D) All options all reasonable. Patient's comorbidities will help is deciding between the above options

Answer: B

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.

Chronic Myeloid Leukemia : Jacob Appelbaum, MD, PhD

Question 1: SJ is a 48-year-old female with chronic phase CML treated with dasatinib 100mg daily. Major molecular response (BCR-ABL1 transcripts £ 0.1%) is achieved at 9 months. This response persists (0.01-0.03% BCR-ABL1 transcripts) on subsequent monitoring at 3-month intervals. Monitoring at 27 months detects BCR-ABL1 transcripts at 0.09%. The patient endorses that she had skipped doses over the past two months due to work-related travel. Repeat studies one month later demonstrate an increase in BCR-ABL1 transcripts to 0.23%. ABL mutation studies to assess resistance identify a V299L mutation.

Appropriate treatment strategies include which of the following?

A) Stop dasatinib and start bosutinib 500mg daily
B) Increase dasatinib to 140 mg daily
C) Stop dasatinib and start nilotinib at 300 mg twice daily
D) Choices A or C

Answer: C

Rationale: V299L confers resistance to bosutinib and dasatinib. Increasing dasatinib will not overcome resistance. Patients who develop resistance mutations are more likely than those without resistance mutations to have molecular recurrence with other mutations. For nilotinib irreversible complications include cerebrovascular, cardiovascular, and peripheral arterial occlusive events. Across retrospective studies, events have occurred in 10-20% of nilotinib-treated patients, and consequently monitoring of cardiovascular risk factors is recommended.

Question 2: TS is a 52-year-old male with no other medical problems diagnosed with chronic phase CML and started on bosutinib 400mg daily. Blood counts normalize over 4 weeks. At 3 months after initiating therapy molecular response is assessed and shows BCR-ABL1 transcripts at 45%. The patient is adherent to therapy and has not missed any doses. You assess for resistance by submitting mutation analysis of ABL by sequencing. ABL mutation studies identify a T315I mutation.

Appropriate treatment strategies include which of the following?

A) Stop bosutinib and start asciminib at 40 mg twice daily
B) Stop bosutinib and start dasatinib 140mg daily
C) Stop bosutinib and start nilotinib 400mg twice daily
D) Stop bosutinib and start ponatinib at 45 mg daily
E) Choices A and D

Answer: D

Rationale: The T315I mutation is resistant to all currently FDA approved ABL-targeted TKIs except ponatinib and asciminib. However, a higher dose of asciminib is needed to effectively treat T315I mutated CML and the FDA approved dose is 200 mg twice daily. Consequently, choice A is incorrect. Based upon the age of the patient, co-morbidities, and response to ponatinib (or asciminib at the correct dose), ponatinib (or asciminib) can be continued or be used as a bridge to transplantation. Enrollment on a clinical trial is also reasonable.

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

Question 1: A 43 year old woman with no significant past medical history presents to the emergency department with a white blood cell count of 15,000/microliter; differential shows 95% myeloid blasts. Cytogenetic analyses demonstrates t(8;21) in all 20 cells. Gemtuzumab ozogamicin is added to her induction chemotherapy regimen due to clinical trials demonstrating improved survival.

Which of the following toxicities would be most likely to be directly related to gemtuzumab ozogamicin?

A) Sinusoidal obstructive syndrome
B) Prolonged QT interval
C) Cerebellar ataxia
D) Diffuse maculopapular rash
E) Differentiation syndrome

Answer: A

Rationale: Newly diagnosed acute myeloid leukemia (AML) is commonly treated with intensive induction chemotherapy in fit individuals. Risk stratification can be performed using the European LeukemiaNet (ELN) 2022 guidelines (Dohner H et al Blood 2022). This patient would be considered favorable-risk due to the finding of t(8;21) on

cytogenetics. In general, patients with favorable-risk leukemia have improved survival when gemtuzumab ozogamicin (GO) is added to induction chemotherapy (meta-analysis of randomized trials: Hills RK et al Blood 2014). However, there are particular toxicities that are associated with GO which need to be considered, including an increased rate of hepatotoxicity via sinusoidal obstructive syndrome (also known as veno-occlusive disease); this is reflected in Answer A. The rate of SOS can be mitigated with fractionated dosing of GO, e.g. administering a dose of 4.5mg/m2 on days 1, 4, and 7. Other toxicities associated with GO include prolonged cytopenias as well as infusion-related reactions.

The other answer choices are commonly seen side effects following chemotherapy. Prolonged QT interval (Answer B) is associated with multiple tyrosine kinase inhibitors, particularly FLT3 inhibitors. Cerebella ataxia (Answer C) is associated with toxicity from high-dose cytarabine; patients with age>60 and/or renal dysfunction are at a higher risk of developing this side effect. Rash (Answer D) is associated with many chemotherapy drugs, but is not particularly associated with GO. Differentiation syndrome (Answer E) can happen with some targeted inhibitors used in AML, but is not associated with GO.

Question 2: A 78 year old man with hypertension and hyperlipidemia presents to his primary care physician with fatigue, and he is found to have pancytopenia. He is referred to hematology/oncology for bone marrow biopsy, which demonstrates 25% myeloid blasts with a normal karyotype and a mutation in IDH1. He starts treatment with azacitidine plus ivosidenib.

What toxicity is he at particular risk for related to the ivosidenib?

A) Sinusoidal obstructive syndrome
B) Prolonged QT interval
C) Cerebellar ataxia
D) Diffuse maculopapular rash
E) Differentiation syndrome

Answer: E

Rationale: In older individuals, the risk/benefit ratio of intensive induction chemotherapy is not always favorable. One option for treatment of patients with an IDH1 mutation is initiation of an IDH1 inhibitor in combination with the hypomethylating agent azacitidine (Montesinos P et al NEJM 2022). While this regimen has not been directly compared to azacitidine and venetoclax, it appears to be better-tolerated with a low level of cytopenias. However, there are particular toxicities associated with IDH inhibitors that need to be considered, particularly differentiation syndrome (Answer E), which can occur up to 100 days after initiation of the IDH inhibitor.

The other answer choices are commonly seen side effects following chemotherapy. Sinusoidal obstructive syndrome (Answer A) can be associated with gemtuzumab

ozogamicin and/or myeloablative conditioning regimens. Prolonged QT interval (Answer B) is associated with multiple tyrosine kinase inhibitors, particularly FLT3 inhibitors. Cerebella ataxia (Answer C) is associated with toxicity from high-dose cytarabine; patients with age>60 and/or renal dysfunction are at a higher risk of developing this side effect. Rash (Answer D) is associated with many chemotherapy drugs, but is not particularly associated with IDH inhibitors.

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.

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 : Andrew Portuguese, MD

Question 1: A 54yo woman presents for a second opinion. Her prior Onc team recently diagnosed her with MM and are recommending treatment with 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. 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 end organ dysfunction, lytic lesions, or other myeloma-defining features (ie, ≥60% plasma cells, free kappa/lambda >100, bone lesions).

Question 2: A 71yo man has routine yearly labs dran 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 >3% of people who are ≥50 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. Skeletal survey 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.

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. She started treatment with CyBorD (cyclophosphamide, bortezomib, dexamethasone) 1 month ago. She walks several miles per day and has no significant comorbidities.

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

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

Answer. C.

Rationale: Switch to isa-VRd (isatuximab, bortezomib, lenalidomide, dex). Quad therapy is preferred among transplant ineligible patients with NDMM

Relapsed/Refractory Myeloma & Amyloidosis : Andrew J. Cowan, MD

Question 1: You are seeing a 56 year old female with relapsed multiple myeloma. She was diagnosed 5 years ago, presenting with R-ISS stage 1 disease, with no high risk disease markers evidence. She underwent initial treatment with Daratumumab, bortezomib, lenalidomide, and dexamethasone (D-RVD) followed by autologous stem cell transplantation. She received maintenance therapy with lenalidomide alone, until she has recently shown evidence for progression. She is currently asymptomatic. She has a monoclonal protein of 0.3 g/dl, and serum free light chain involved of 12.2 mg/dl. PET-CT shows an area of FDG uptake in the left humerus, SUV 5.6, with associated new lytic lesion.

Should this patient receive treatment for relapsed multiple myeloma?

A) Yes; there is an elevated monoclonal protein
B) No; the monoclonal protein is < 0.3 g/dl
C) Yes; there is evidence for clinical disease relapse
D) No, the patient is asymptomatic

Answer: C.

Rationale: This patient has clinical disease progression with a new osteolytic bone lesion. Despite having a low monoclonal protein and absence of symptoms, she should be treated for relapse.

Question 2: A 67 year old male with relapsed multiple myeloma is seen in your clinic. He has had 2 lines of therapy, including upfront treatment with lenalidomide, bortezomib, and dexamethasone, followed by autologous stem cell transplantation, and then treatment with daratumumab, bortezomib, and dexamethasone. He is clinically progressing and needs to initiate a new line of therapy. He does not otherwise have any significant medical comorbidities. Which of the following are approved therapies that he could receive?

A) Daratumumab, carfilzomib, and dexamethasone
B) Idecaptagene vicleucel (Abecma)
C) Ciltacabtagene autoleucel (Carvykti)
D) Teclistamab
E) Options A-C

Answer: E

Rationale: Although not ideal, option A, Daratumumab, carfilzomib and dexamethasone could be used, based on the results of the Candor trial (PMID: 34871550). Idecaptagene vicleucel (Abecma) is FDA approved for > 2 lines of therapy, and Ciltacabtagene autoleucel, Carvykti, is approved for > 1 line of therapy. Teclistamab is only approved for > 4 lines of therapy.

Question 3: A 62 year old female is seen in hematology oncology clinic for a plasma cell dyscrasia. 2 months ago, she presented initially with proteinuria, and was found to have 2.4 g protein, predominantly albumin, on a 24 hour urine collection. Physical examination reveals bilateral edema and bibasilar crackles, and periorbital ecchymoses. Serum free light chain analysis showed a kappa of 2.3 mg/dl, lambda 13.1 mg/dl, and ratio of 5.69. SPEP showed a 0.1 g/dl lambda free light chains. Serum creatinine was 0.8 mg/dl, and alkaline phosphatase is normal. Serum NT-pro BNP is elevated at 2799 ng/Ml and TTE shows an EF of 56% with septal hypertrophy. A bone marrow biopsy shows 5% lambda clonal plasma cells, and a Congo red stain on the bone marrow revealed Congophilic deposits, apple green birefringence in the vessel walls.

What is the best initial treatment for this patient, based on a randomized phase 3 trial, given the diagnosis?

A) Daratumumab, bortezomib, cyclophosphamide, and dexamethasone (Dara CyBorD)
B) Daratumumab, lenalidomide, bortezomib, and dexamethasone (Dara RVd)
C) Bortezomib, lenalidomide, and dexamethasone (RVd)

D) Bortezomib, cyclophosphamide, and dexamethasone (CyBorD)
E) Options A and D

Answer: A.

Rationale: The best initial treatment for AL amyloidosis, based on the phase 3 randomized trial (ANDROMEDA study), is daratumumab, bortezomib, cyclophosphamide, and dexamethasone (Dara-CyBorD). This combination was shown to significantly improve hematologic response rates and organ function in patients with AL amyloidosis compared to CyBorD alone.

Friday, September 27

Inherited & Acquired Marrow Failure : Bart L. Scott, 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.

Thalassemia & Hemoglobinopathies : Kleber Yotsumoto Fertrin, MD, PhD

Question 1: A 34yo F is diagnosed with stage IA mediastinal large B-cell lymphoma and is noted to have anemia. White blood cell differential is normal.

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) Iron deficiency anemia
D) Needs labs to distinguish iron deficiency and anemia of inflammation

Answer: A

Rationale: Beta thalassemia trait causes HbA2 elevation, not decrease. Decreased HbA2 can be found in iron deficiency or alpha thalassemia. Iron deficiency or anemia of inflammation restrict iron and therefore cause low RBC counts, particularly if enough to cause significant microcytosis. Therefore, the only correct option is alpha thalassemia trait.

Question 2: A 19-yo M with beta thalassemia major is referred to the clinic to establish care after moving for college. He had been on chronic transfusions since age 1 every 3-4 weeks, but he has missed a few appointments during the move. His hemoglobin is 8.0g/dL, hematocrit 24%, MCV 82fL, MCH 29pg, reticulocytes 6%, WBC and platelets within normal limits. He is asymptomatic other than feeling a little more fatigued when playing basketball. He continues to take folic acid and deferasirox for iron chelation.

What is the recommendation to manage his anemia?

A) No need for transfusion and no change in medications
B) No need for transfusion and start luspatercept
C) Transfuse 1 red blood cell unit to achieve hemoglobin between 9.5-10.5g/dL
D) Transfuse 3 red blood cell units to achieve hemoglobin 11-12g/dL

Answer: D

Rationale: Beta thalassemia major patients should be transfused to keep pre-transfusion hemoglobin between 9.5-10.5 and keep post-transfusion around 11-12g/dL but under 13-15g/dL after transfusion to suppress ineffective erythropoiesis. Luspatercept should not be used as a substitute for transfusions, but to reduce the overall need for transfusions.

Question 3: A 23-year-old F with HbSS is admitted for pain crisis with Hb 5.5g/d. She is discharged after proper pain control and transfusion of 2 pRBC units. She returns 10 days later reporting extreme fatigue and dark urine, with Hb 4.5g/dL. On exam, there is extreme pallor and jaundice, but she is hemodynamically stable. LDH is 980 U/L, DAT and screen are positive for an anti-C.

What is the most appropriate treatment?

A) Transfuse to Hb>6g/dL with C-negative RBC units
B) Start corticosteroids and eculizumab
C) Start corticosteroids and IVIg
D) Red cell exchange with C-negative RBC units

Answer: C

Rationale: This patient has hyperhemolysis syndrome as a complication of a delayed hemolytic reaction with a new anti-C antibody. 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.

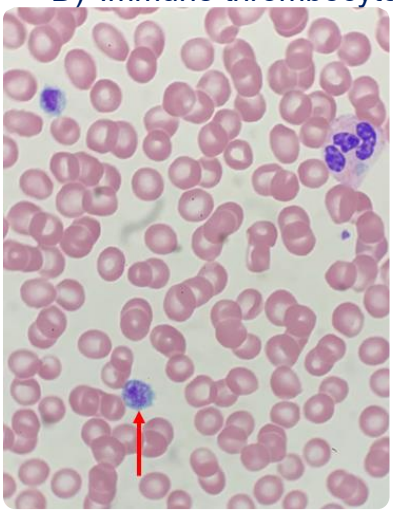
Thrombocytopenia : Sandhya Panch, MD, MPH

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

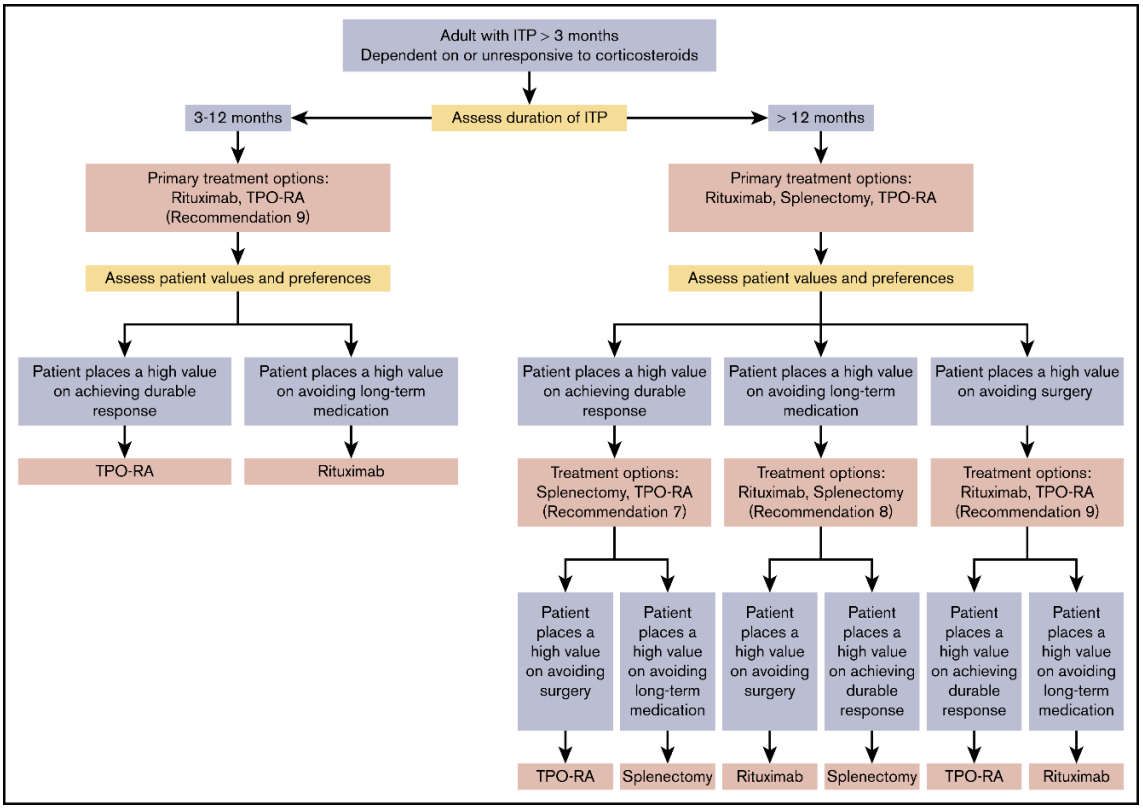
Rationale: Personal and family history suggest an inherited bleeding disorder ruling out ITP. Failure to steroids also points against an acquired autoimmune condition like ITP. Inclusion bodies in the WBCs, large platelets in low numbers and hearing loss are characteristic of a syndromic macrothrombocytopenia,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

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) Continue rivaroxaban without interruption.
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 V TE 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.

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 : Nicholas Burwick, MD

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.