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Hematopoietic Stem Cell Transplantation

Rachel B. Salit

Fred Hutchinson Cancer Research Center

Seattle, WA

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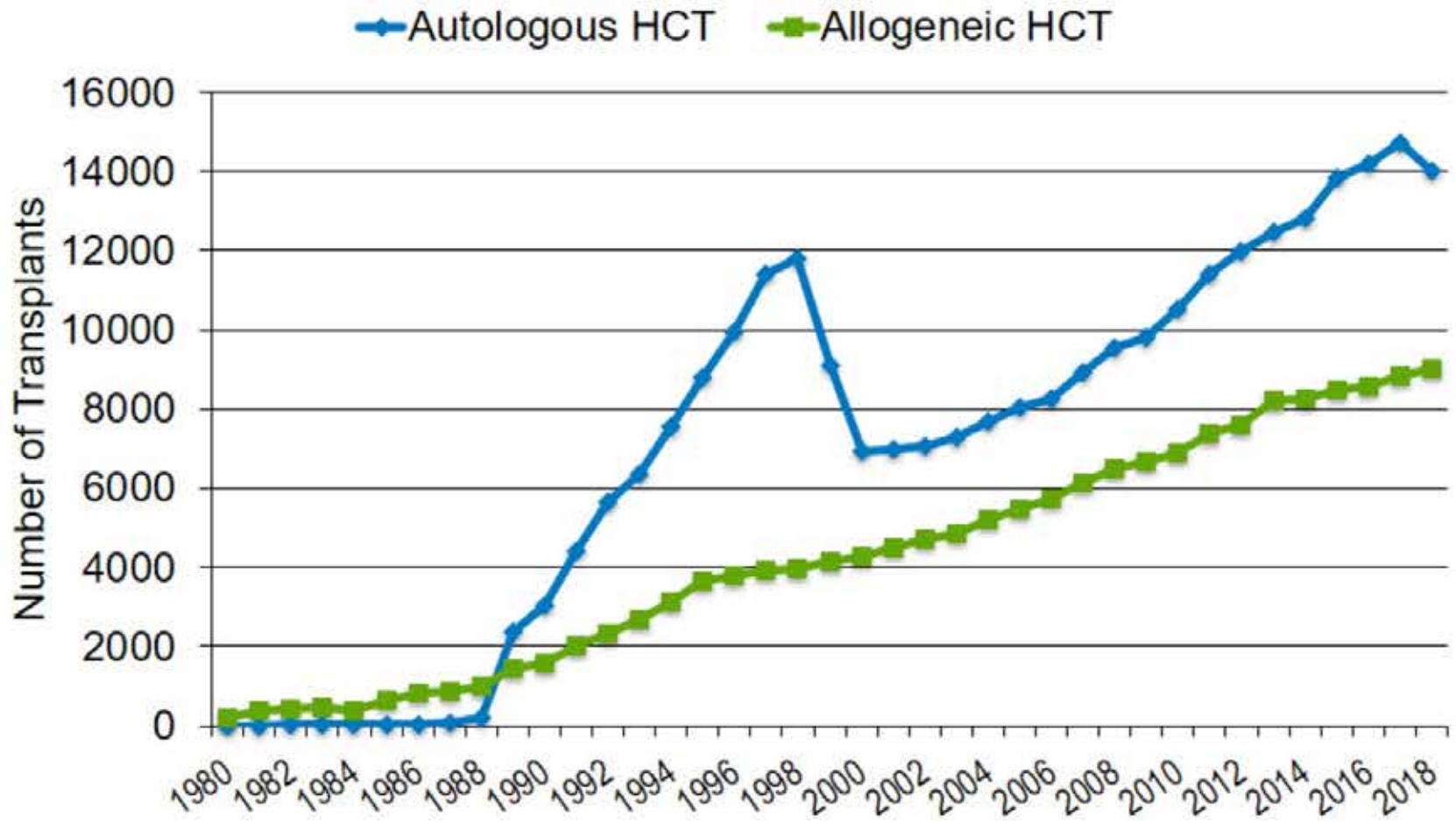
Outline

- Indications for Hematopoietic Stem Cell Transplant (HCT)
- Donor and Cell Sources
- Conditioning Regimens
- Complications
  - Regimen Related Toxicity
  - GVHD
  - Infections
  - Late Effects
  - Relapse

Annual Number of HCT Recipients in the US by Transplant Type



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Indications for Transplant

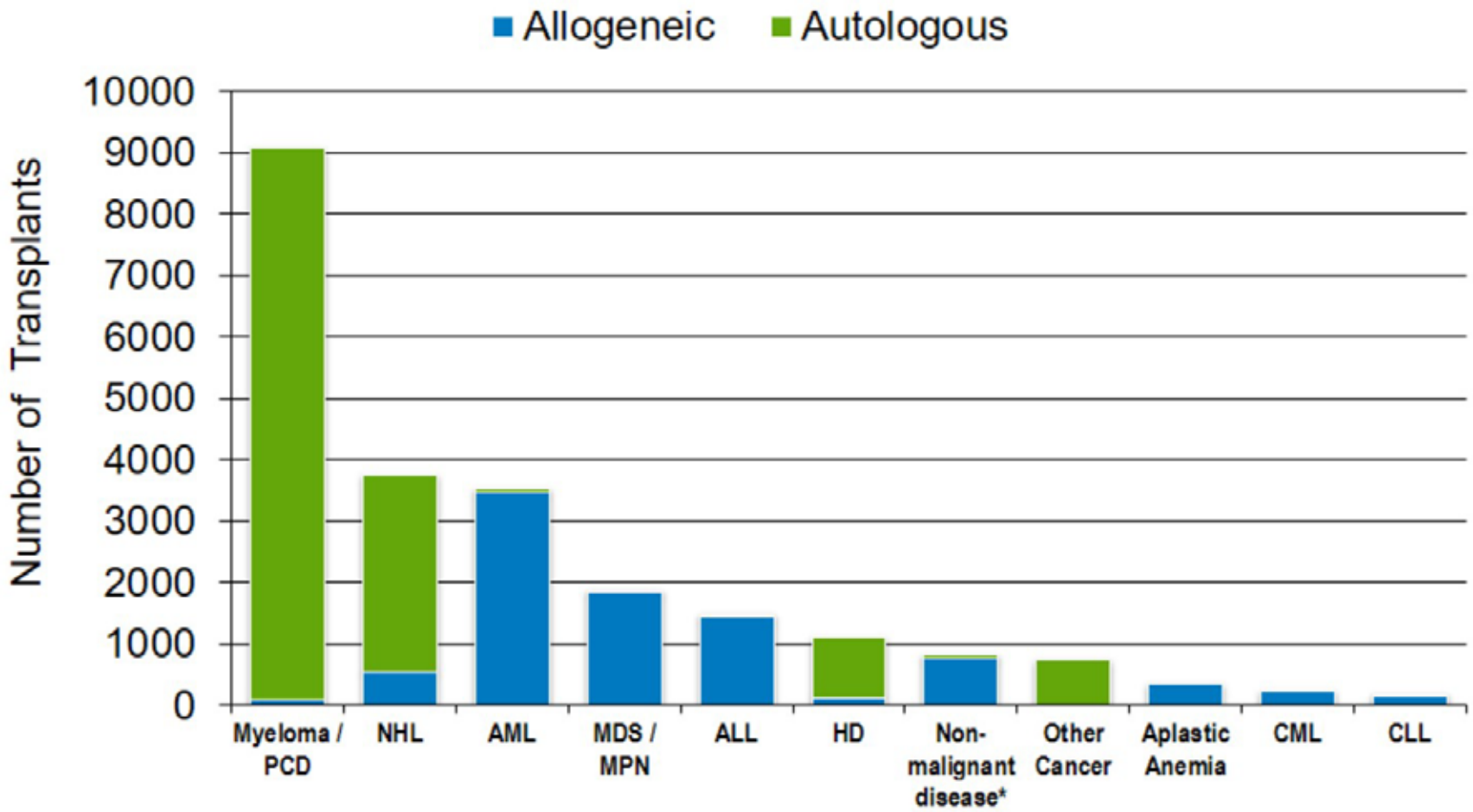
Malignant

- Acute Myeloid Leukemia
- Acute Lymphocytic Leukemia
- Myelodysplastic Syndrome
- Chronic Myeloid Leukemia
- Myeloproliferative Disease
- Chronic Lymphocytic Leukemia
- Multiple Myeloma
- Hodgkin Lymphoma
- Non-Hodgkin's Lymphoma

Non-Malignant

- Immunodeficiencies
- Aplastic Anemia
- Hemoglobinopathies
- Enzymatic Disorders
- Autoimmune Diseases

Indications for Hematopoietic Cell Transplant in the US, 2018



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*excludes aplastic anemia.

Autologous Transplant

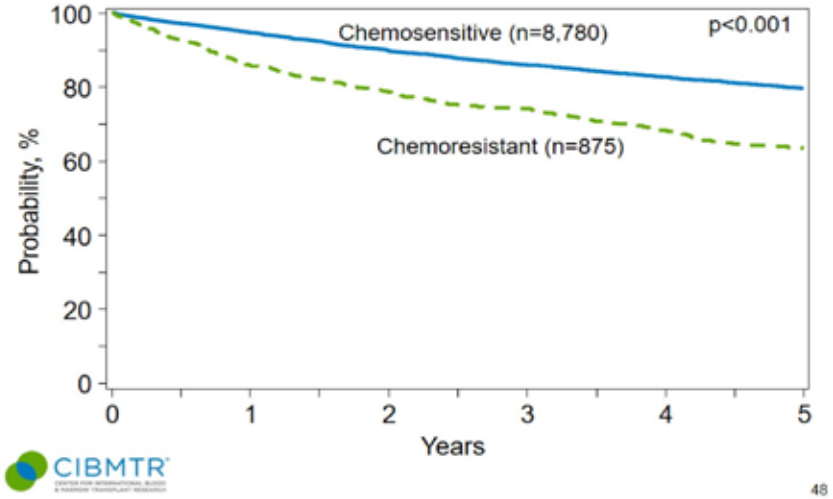
- Disease targeted myeloablative chemotherapy and followed by rescue with their own previously saved stem cells.
- Auto-stem cells are collected from GCF or chemo-mobilized peripheral blood.
- If the patient fails to mobilize, plerixafor may be administered
- Frozen cells may be used more than 10 years later without change in CD34+ viability.
- Treatment-related mortality rate < 1%-3%.

Multiple Myeloma

- Auto HCT improves survival in patients < 65 years old with newly diagnosed multiple myeloma.
- Progression free survival is longer if patients have HCT earlier rather than waiting for first relapse.
- Maintenance with lenalidomide or bortezomib further improves PFS.

Lymphoma

Survival after Autologous HCT for Hodgkin Disease, 2007-2017



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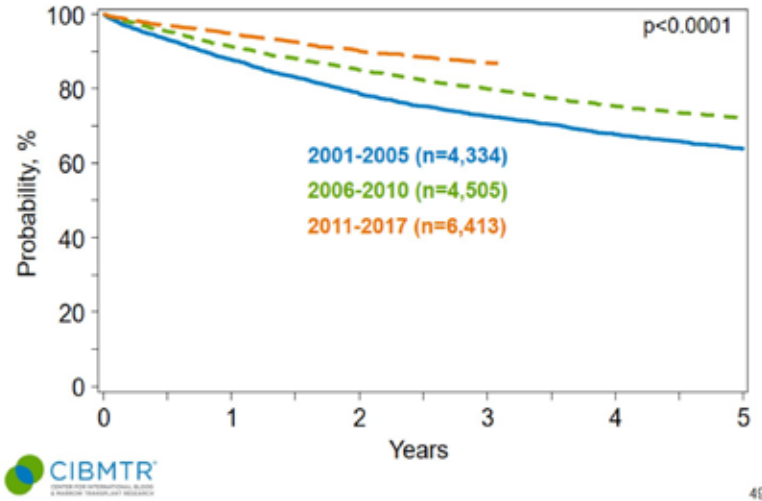
Trends in Survival after Autologous HCT for HD, 2001-2017



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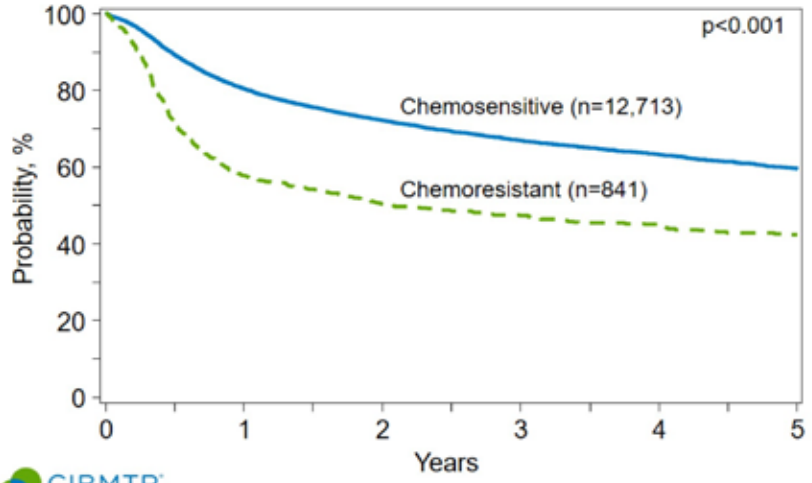
Survival after Autologous HCT for Diffuse Large B-Cell Lymphoma (DLBCL), 2007-2017



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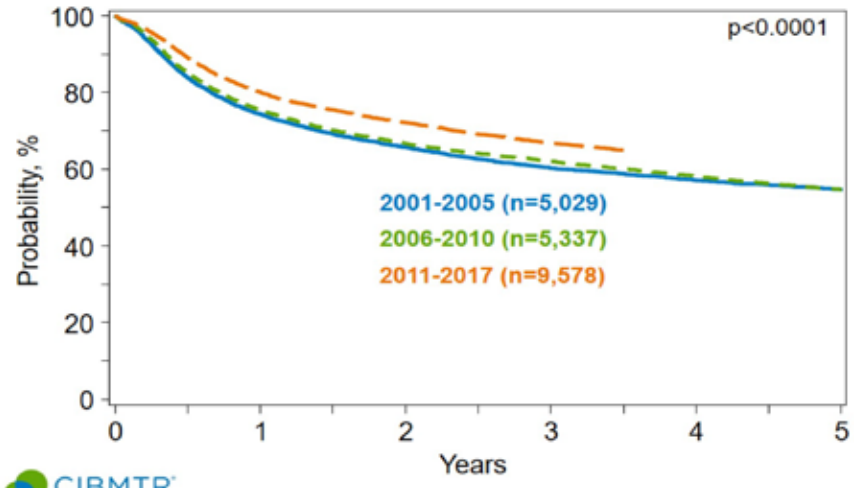
Trends in Survival after Autologous HCT for DLBCL, 2001-2017



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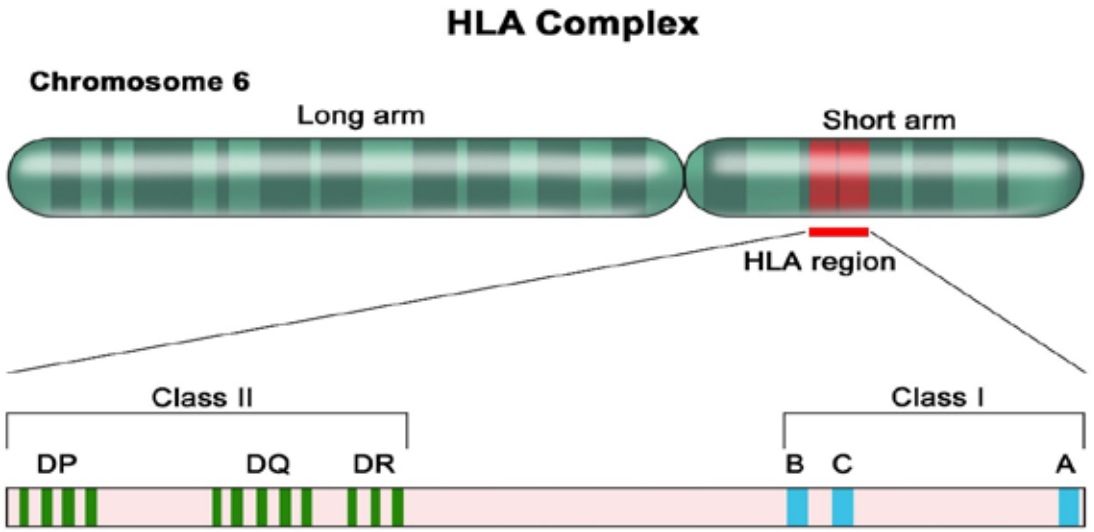
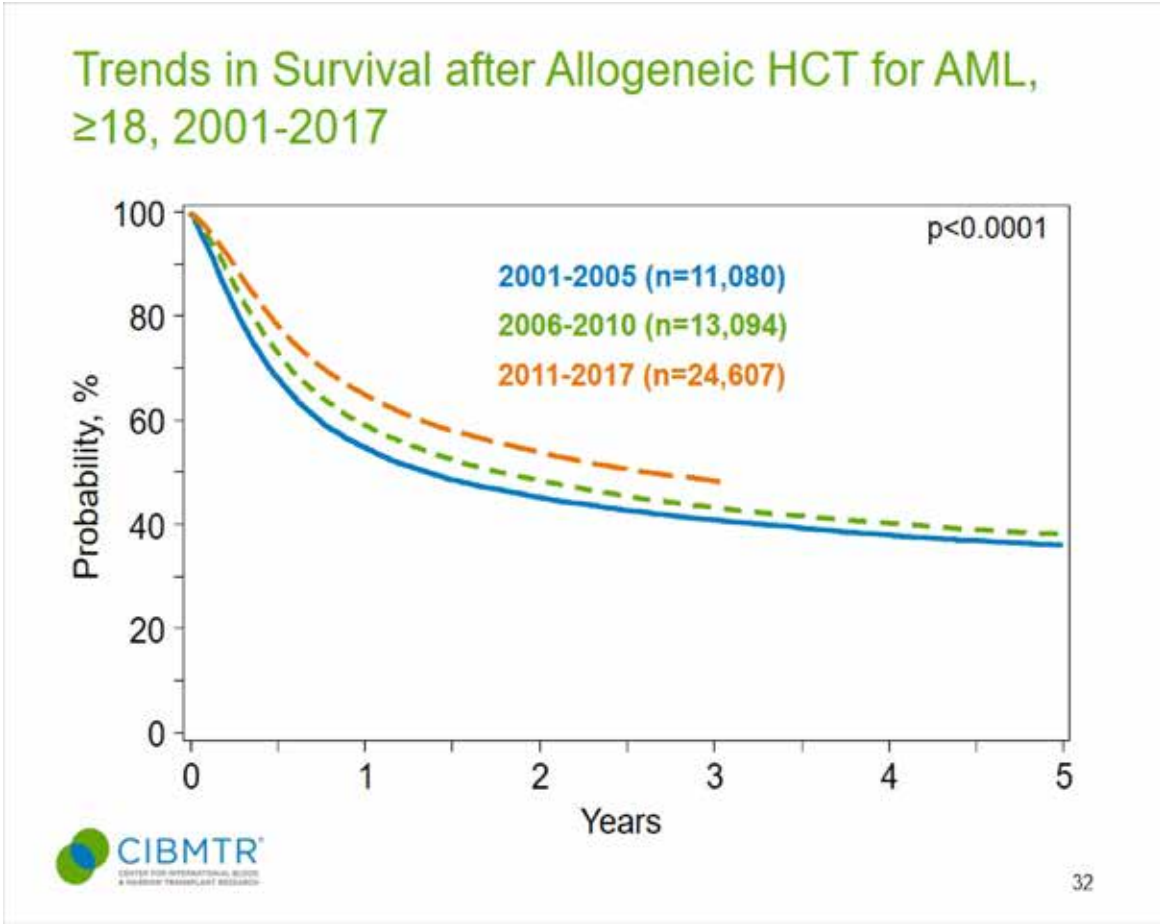
Allogeneic Transplant

- Utilizes both chemo/radiotherapy and graft versus tumor effect.
- HLA is encoded by the Major Histocompatibility Complex on chromosome 6.
- Even if individuals are HLA matched at major antigens (10 of 10), they are likely to be mismatched at the minor antigens.



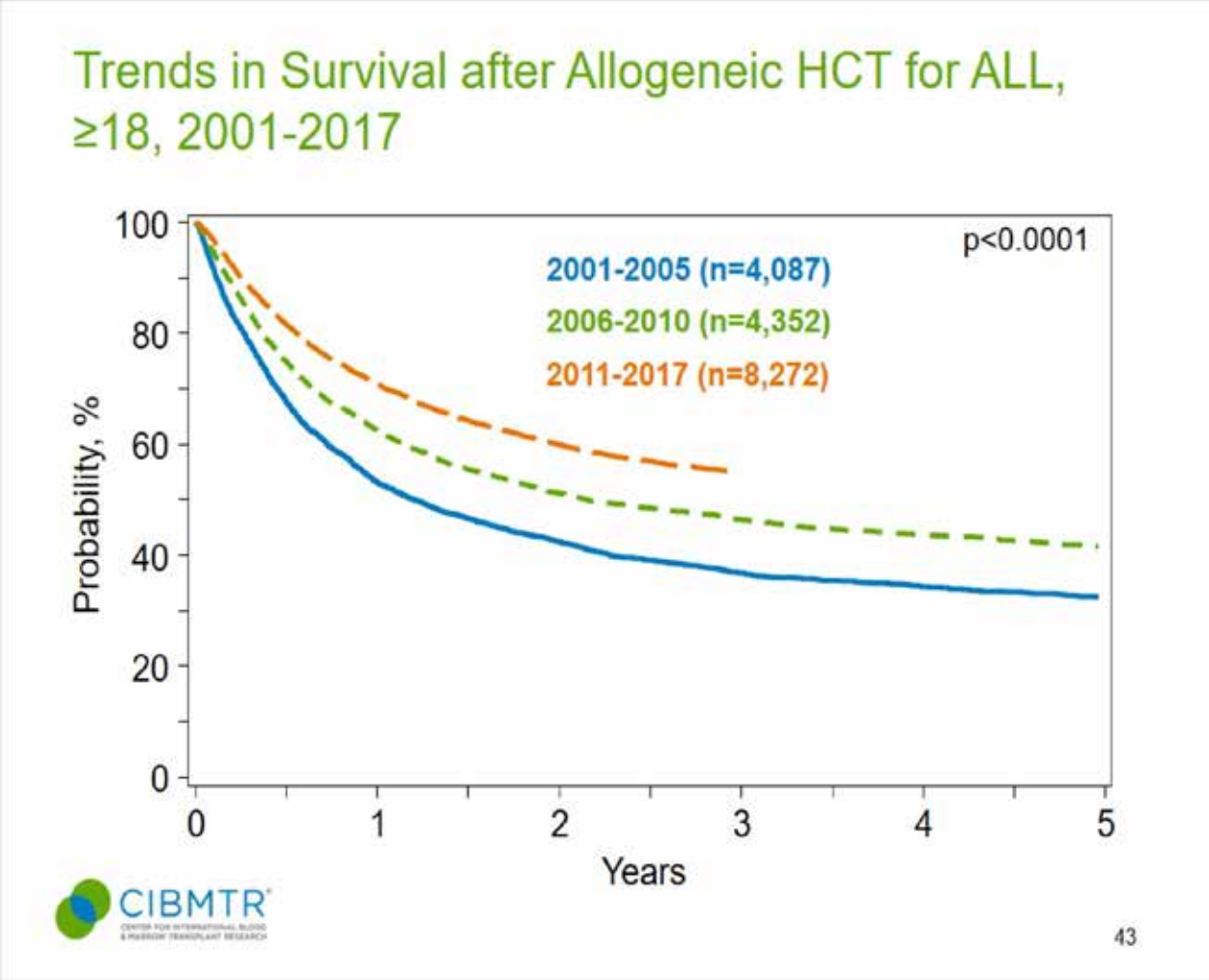
Acute Myeloid Leukemia (AML)

- Allo-HCT consistently achieves 5-year disease free survival of 50-70% for patients in first remission.
- Advantages of transplantation are most apparent for patients with unfavorable and intermediate risk leukemia.
- Cure rates decrease if patients are transplanted in second complete remission but are still better than expected for chemotherapy alone.



Allo HCT for ALL

- Long-term survival is improved with allo-HCT for patients with high-risk disease including MLL, Philadelphia chromosome positive (Ph+) and patients who are delayed in achieving remission beyond the first cycle of induction chemotherapy.
- Results with Ph+ ALL have improved with the availability of tyrosine kinase inhibitors (TKIs), but HCT remains superior to chemotherapy.



Allo-HCT for Myelodyplastic Syndrome (MDS) and Myeloproliferative Disease (MPN)

- MDS and MPN are generally incurable except with Allo-HCT
- HCT is reserved for patients with advanced stage disease.
- Current guidelines recommend allo-HCT be considered for:
  - Patients up to age 65
  - Intermediate 2 or higher risk according to the D(IPSS(R)).
- Patients with MPN have higher rates of graft failure than more other malignant diseases.

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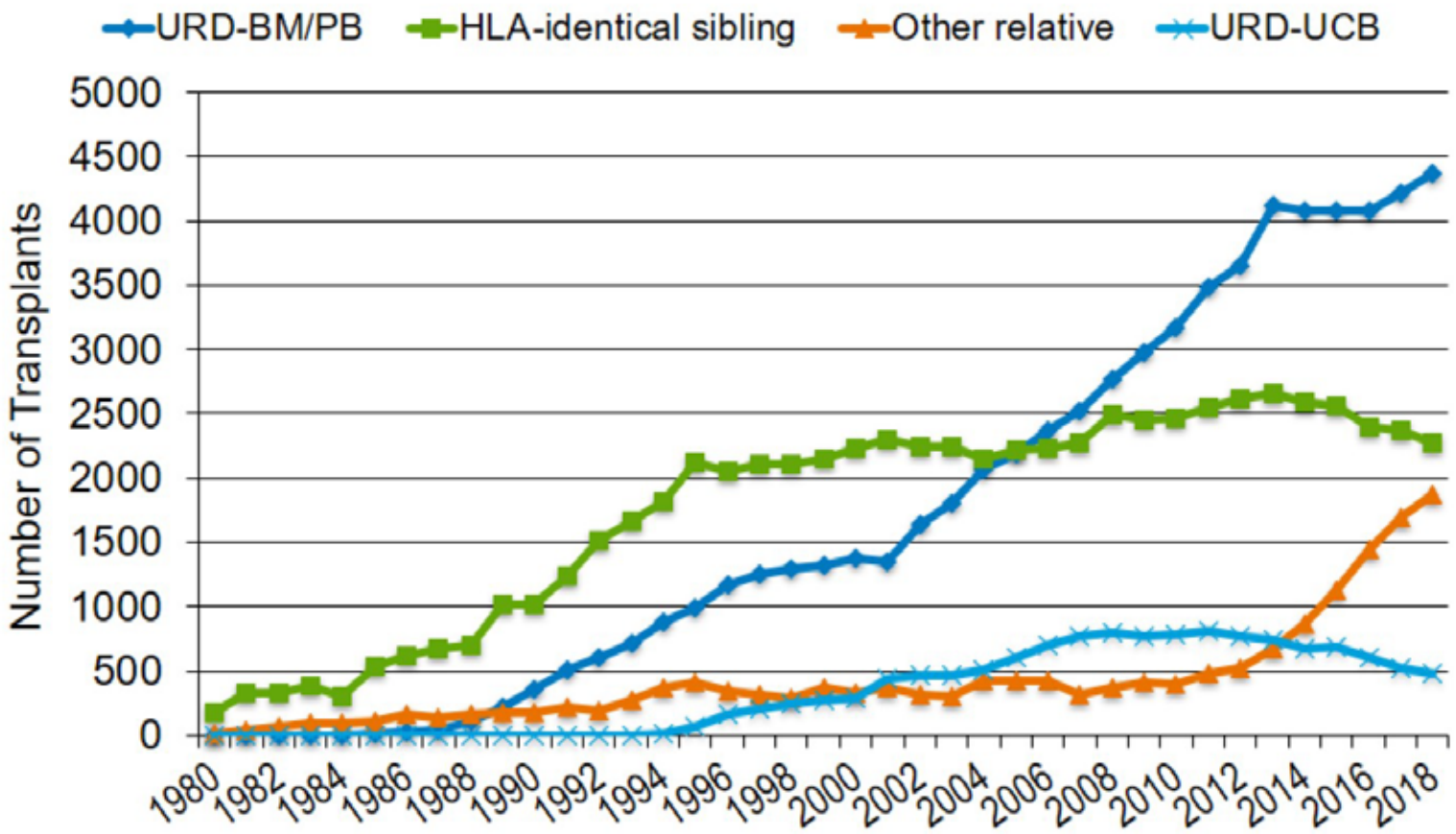
Donor and Cell Sources

Allogeneic HCT Recipients in the US, by Donor Type



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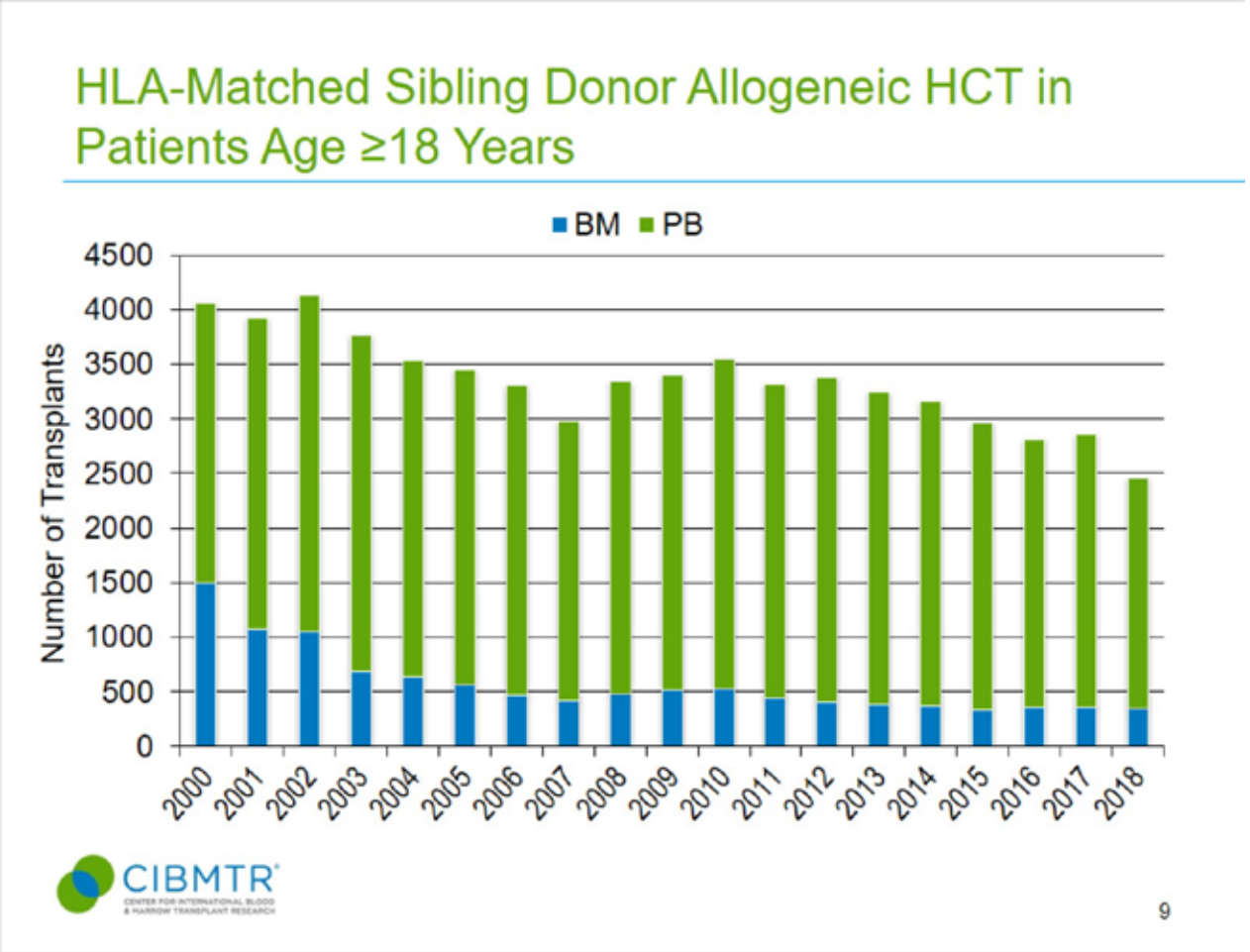
Bone marrow (BM) vs PB (Peripheral Blood)

- Use of PB accelerates engraftment by about 7 days without increasing acute GVHD.
- PB has a higher proportion of T-cells than marrow.
- Chronic GVHD may be higher with PB than BM but disease recurrence appears to be less and survival equivalent

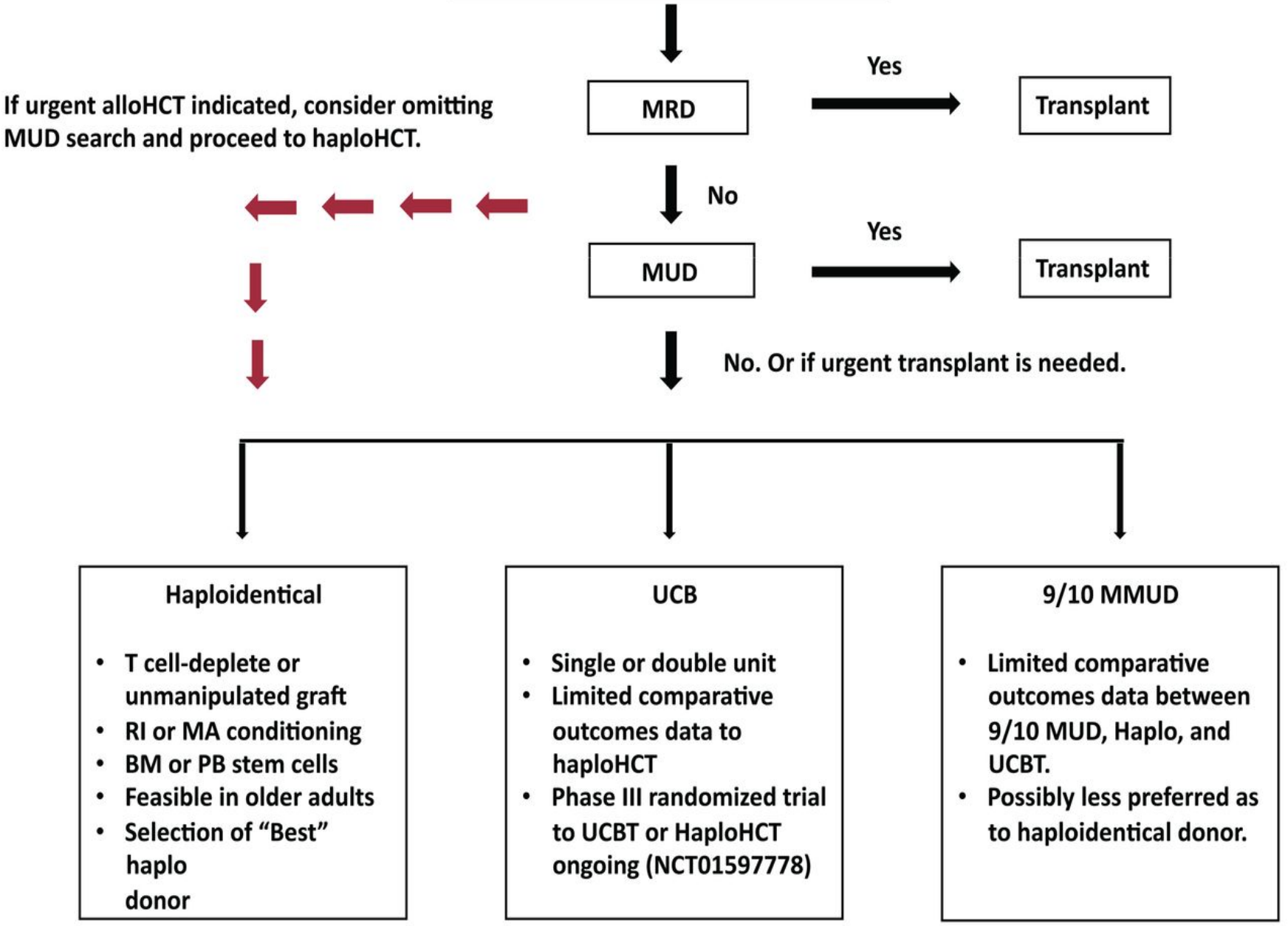


BMT vs PBSCT in Unrelated Donors

- BMT with PBSCT following myeloablative regimen and methotrexate/calcineurin inhibitor for GVHD prophylaxis.
- Faster engraftment but more chronic GVHD with PBSCT.
- Survival was equivalent, but given the higher incidence of chronic GVHD, this study would favor the use of marrow.
- However, this is not being done in clinical practice.

Anasetti C, Logan BR, Lee SJ, et al. Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors. New Engl J Med 2012;367:1487-96.

Patient in need of transplant



Umbilical Cord Blood

- Fewer mature T-cells = less stringent matching criteria
- Allow HLA 4/6 with antigen matches at A and B and allele match at DR
- Data looking at HLA-C suggest improved OS with 5/8 or greater.
- Other advantages include:
  - Rapid availability
  - Potential GVT effect especially when 2 cords are used.
- Disadvantages include:
  - Slower engraftment and immune recovery.
  - Increased viral, bacterial and fungal infections early.
  - Higher incidence of graft failure.
  - Inability to go back to the donor in the event of relapse.

Haploidentical Donors

- Any patient with a living parent or child has a potential Haplo donor.
- Siblings or half-sibling have 50% chance of sharing a haplotype with the patient.
- Advantage of Haplo donors:
  - –Ability to go back to the donor.
  - –Very low chronic GVHD with post transplant Cytoxan.
- Disadvantage of Haplo donors:
  - Higher relapse rate.
  - Increased risk of infections due to T-Cell depletion.
  - Increased graft failure.

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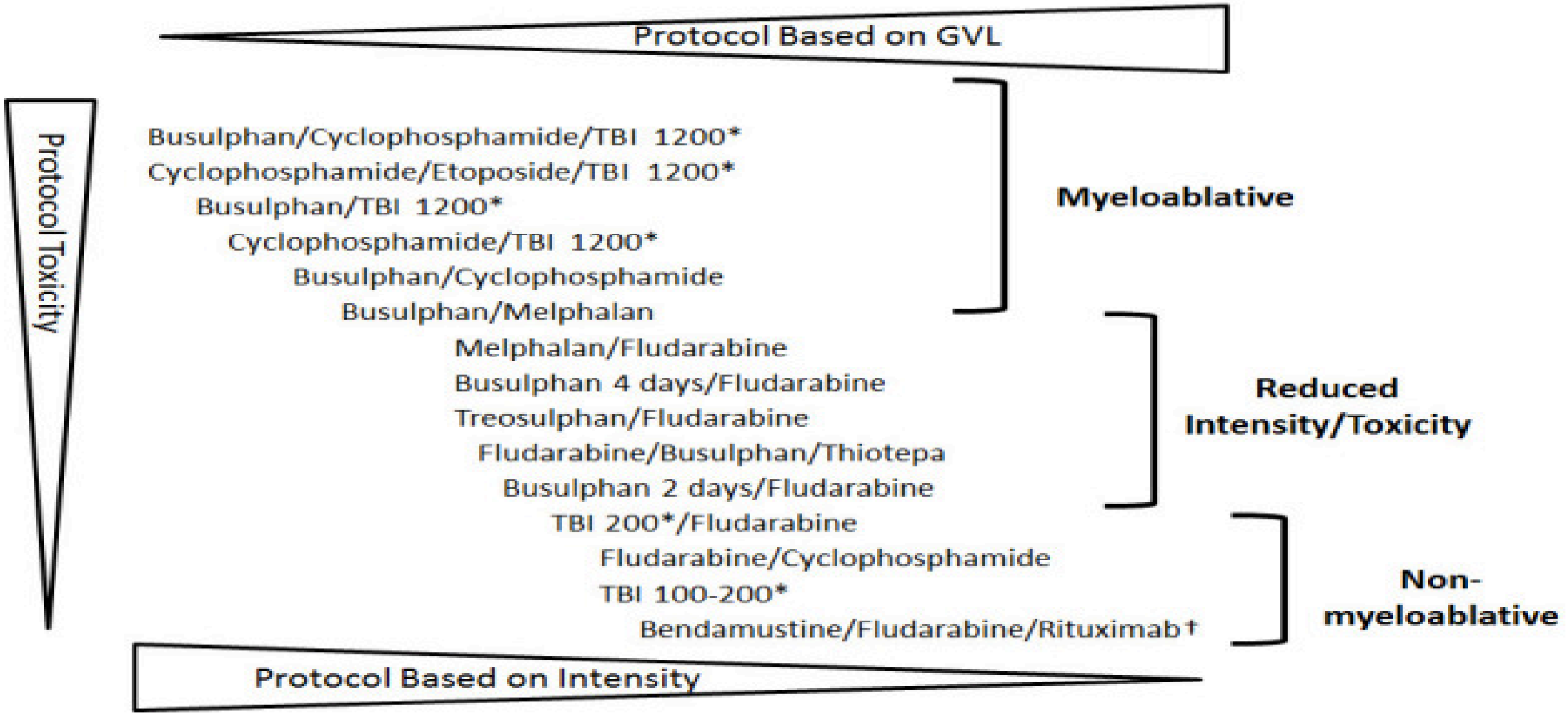
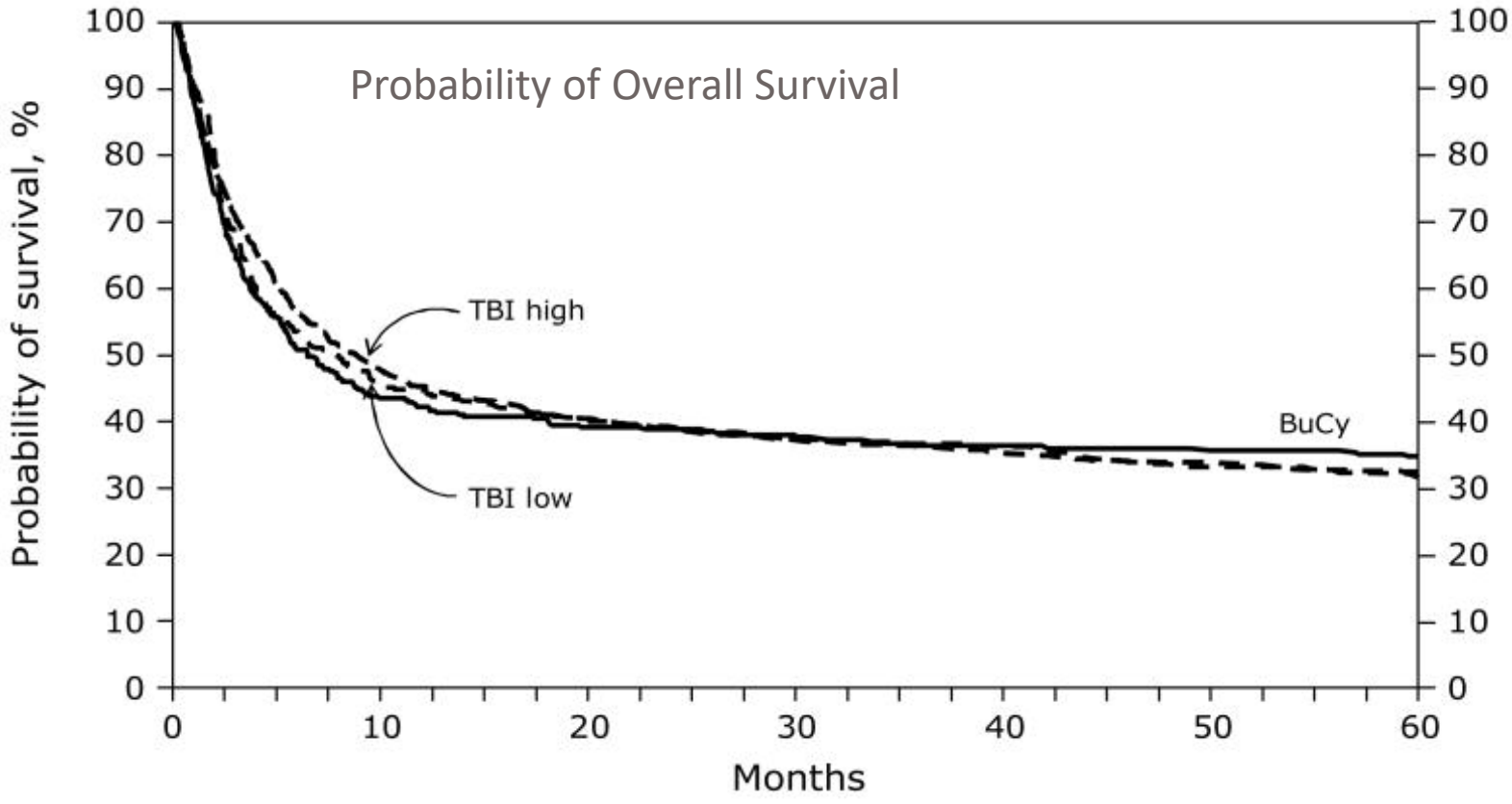
Conditioning Regimens


Protocol Based on GVL
Protocol Toxicity
Busulphan/Cyclophosphamide/TBI 1200*
Cyclophosphamide/Etoposide/TBI 1200*
Busulphan/TBI 1200*
Cyclophosphamide/TBI 1200*
Busulphan/Cyclophosphamide
Busulphan/Melphalan
Myeloablative
Melphalan/Fludarabine
Busulphan 4 days/Fludarabine
Treosulphan/Fludarabine
Fludarabine/Busulphan/Thiotepa
Busulphan 2 days/Fludarabine
Reduced Intensity/Toxicity
TBI 200*/Fludarabine
Fludarabine/Cyclophosphamide
TBI 100-200*
Bendamustine/Fludarabine/Rituximab†
Non-myeloablative
Protocol Based on Intensity

Myeloablative Conditioning (MAC)

- Cytoxan 120mg/kg + 1200 CGy total body irradiation (TBI).
- Busulfan 16mg/kg + Cyclophosphamide 120mg/kg
  - Targeting Busulfan levels in the plasma may decrease the risk of relapse and severe regimen related toxicities.



Uberti et al BMT 2010

Reduced Intensity Conditioning (RIC)

- RIC regimens are selected for:
  - –Older patients
  - –Those with significant comorbidities
  - –Those who have received prior therapy thought to limit their ability to tolerate high dose regimens.
- RIC is associated with less toxicity than MAC but higher relapse rates
- Recovery of hematopoiesis would be expected without the support of hematopoietic progenitor cells.

3 yr Nonadjusted Outcomes

	FluBu2 (N=71)	FluBu4 (N=51)	p-value
TRM	24%	10%	0.06
Relapse	43%	36%	0.5
OS	39%	62%	0.02
DFS	34%	54%	0.04

Non-Myeloablative Conditioning

- Examples of NMA conditioning include:
  - Fludarabine 90mg/m2 + 200cGy or
  - 200-300 cGy TBI alone.
- NMA regimens cause minimal marrow suppression
- Depend on pre and post transplant immune suppression to prevent graft rejection.
- Efficacy of the treatment is largely from a graft versus tumor response.
- Relapse risk is lowest in patients who develop acute or chronic GVHD.

Engraftment

- Defined as the first day of three days of ANC > 500.
- Approximately day +14 post HCT with peripheral blood.
- Delayed by 4-6 days if bone marrow or CB is the source.
- Rate of myeloid recovery can be accelerated by ~7 days with GCSF with marrow and CB.
- GCSF has less of an effect with peripheral blood.
- Chimerism refers to the percent donor or recipient DNA found in the marrow or peripheral blood.
  - Whole marrow
  - CD3, CD33, and CD56 in the peripheral blood

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Complications

Chemotherapy regimen related toxicities

- Nausea, vomiting, diarrhea
- Oral mucositis (Patients may require TPN and PCA)
- Alopecia
- Cytopenias
- Sinusoidal obstruction syndrome
- Idiopathic pneumonia syndrome
- Renal Dysfunction

Sinusoidal obstruction syndrome (SOS)

- Timing: 1-4 weeks following conditioning.
- Characterized by: weight gain, ascites, hepatomegaly, jaundice
- Overall incidence 5-15%
- Risk of severe SOS is higher for patients with:
  - Abnormal liver function tests before the HCT
  - Pre-transplant hepatitis
  - High intensity conditioning
  - Use of Busulfan
- Defibrotide may be effective both as prophylaxis and therapy.
  - Used in cases of severe SOS

Idiopathic pneumonia syndrome (IPS)

- Occurs within 30-90 days after conditioning
- 4-12% of patients.
- Thought to be a toxicity related to chemotherapy or radiation
- Risk factors:
  - High dose TBI
  - Pre-existing lung disease
  - Older age
  - Prior chest radiation
- Mortality rate is about 50%
- No available treatments are clearly effective
  - Usually treated with steroids

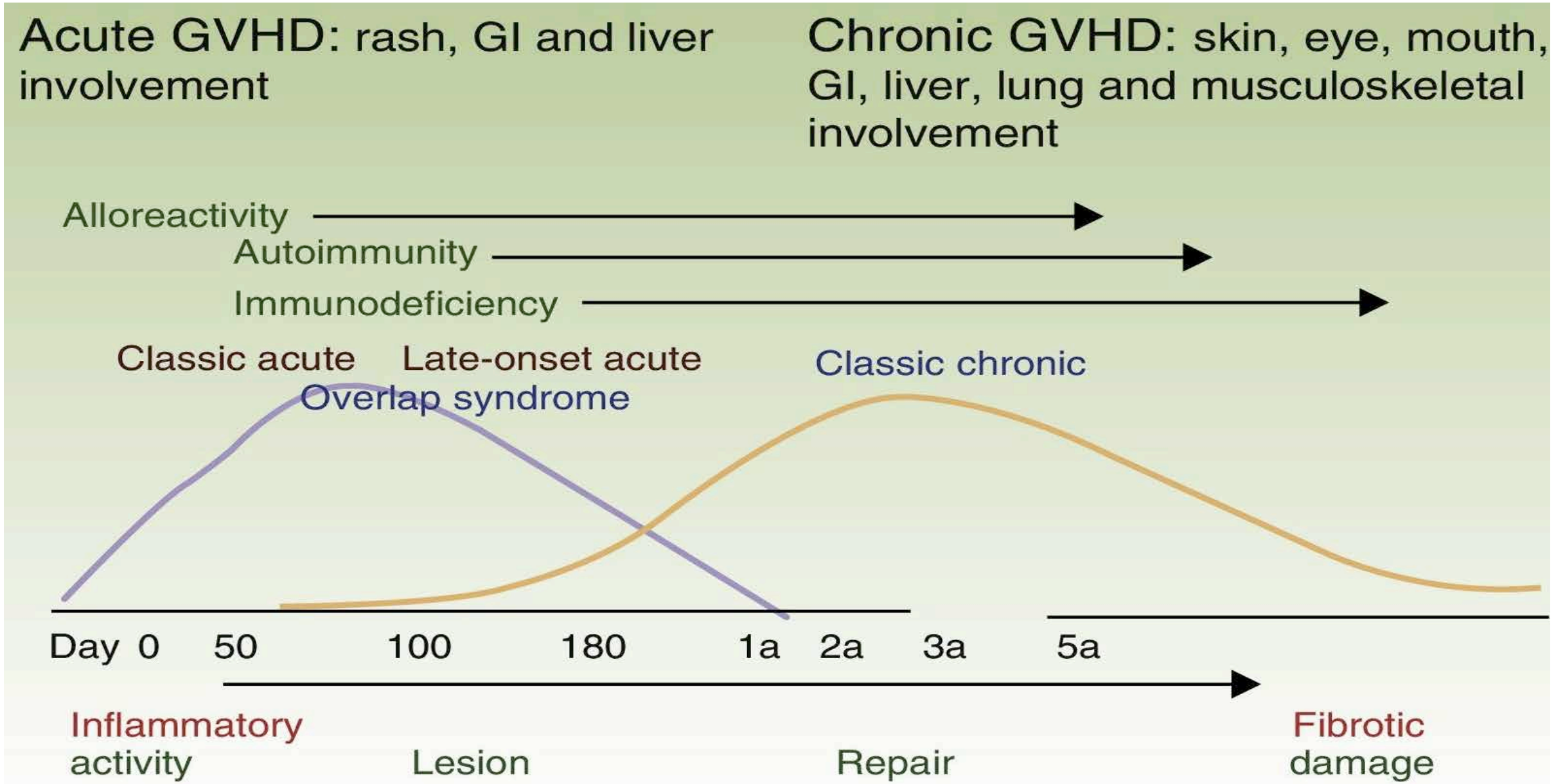
Graft Rejection

- Loss or failure to achieve donor chimerism.
- Result of residual host immune cells rejecting the donor.
- Risk Factors:
  - Increased disparity between donor and recipient.
  - Patients with multiple transfusions and little prior chemotherapy ie. aplastic anemia.
  - T-cell depletion leading to persistence of host immunity.
  - NMA HCT resulting from persistence of host immunity.
  - CBT due to decreased numbers of donor T-cells.

Graft Failure and Poor Graft Function

- Full donor chimerism without recovery of counts.
- Causes include:
  - Prior exposure to stem cell toxins
  - Cell damage during processing and cryopreservation
  - Viral infections
  - Large Spleen
- Patients with graft failure can respond to GCSF.

Graft versus Host disease


Acute GVHD: rash, GI and liver involvement
Chronic GVHD: skin, eye, mouth, GI, liver, lung and musculoskeletal involvement
Alloreactivity
Autoimmunity
Immunodeficiency
Classic acute
Late-onset acute
Overlap syndrome
Classic chronic
Day 0
50
100
180
1a
2a
3a
5a
Inflammatory activity
Lesion
Repair
Fibrotic damage

Acute GVHD Prevention

- Immune Suppression
  - Cyclosporine or tacrolimus + methotrexate
  - MMF + cyclosporine in the NMA setting
  - Addition of sirolimus may further reduce GVHD risk
- T-cell Depletion
  - Positive selection for CD34+
  - Negative selection of CD3+
  - Horse or rabbit ATG
  - Post transplant cyclophosphamide

Acute GVHD characteristics

- Acute (a)GVHD: First 3 months post transplant
- Late Acute GVHD: After 3 months
  - Most commonly when immune suppression is withdrawn.
  - NMA/RIC transplant with late complete donor chimerism.
- Occurs in 30% of patients with HLA-matched sibs and 50-60% with unrelated donors
- Factors associated with increased aGVHD include:
  - HLA-mismatching
  - Older age of patient
  - Multiparous female donor
  - Peripheral blood and
  - More intense conditioning

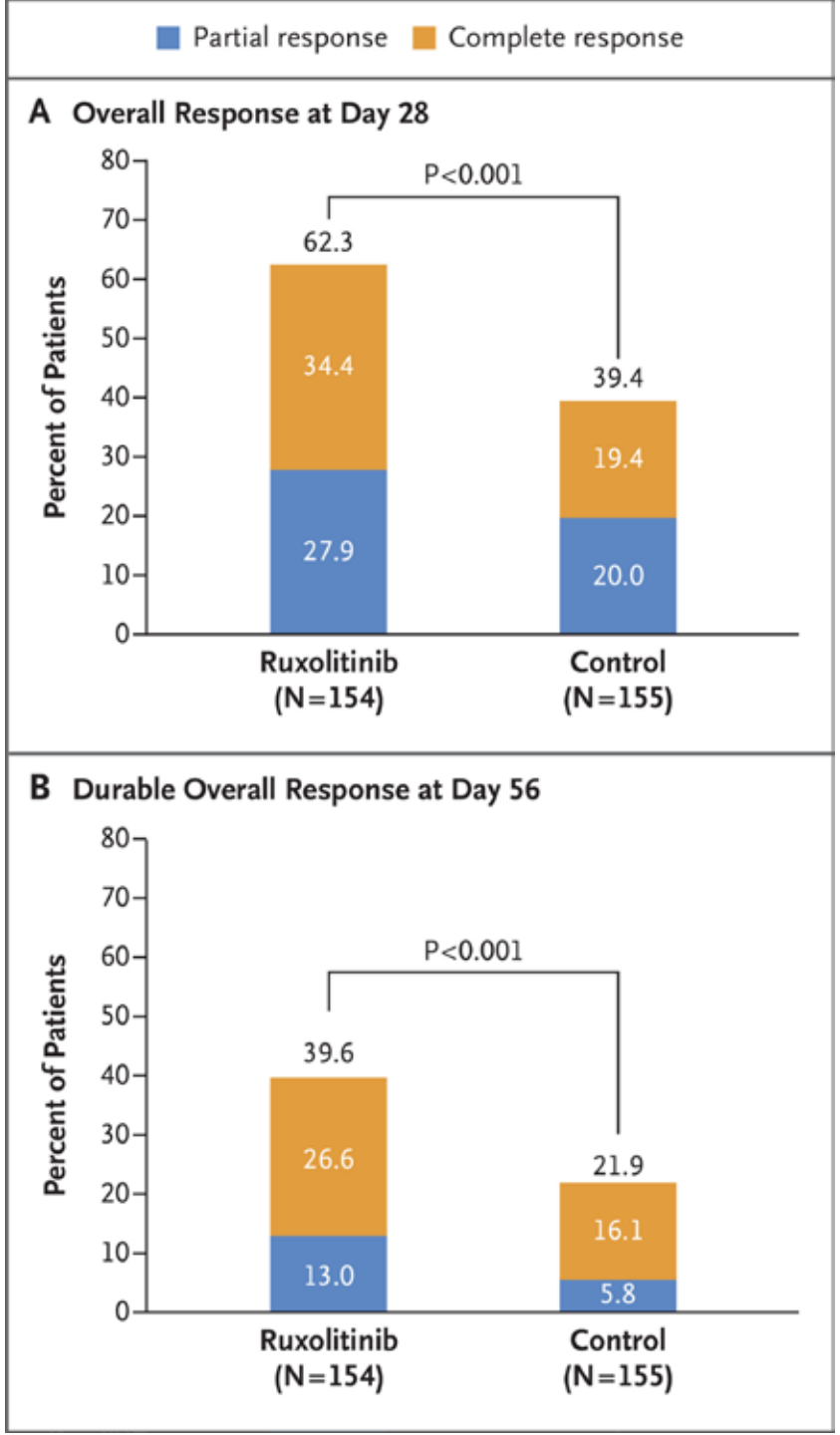
Acute GVHD Manifestations and Scoring

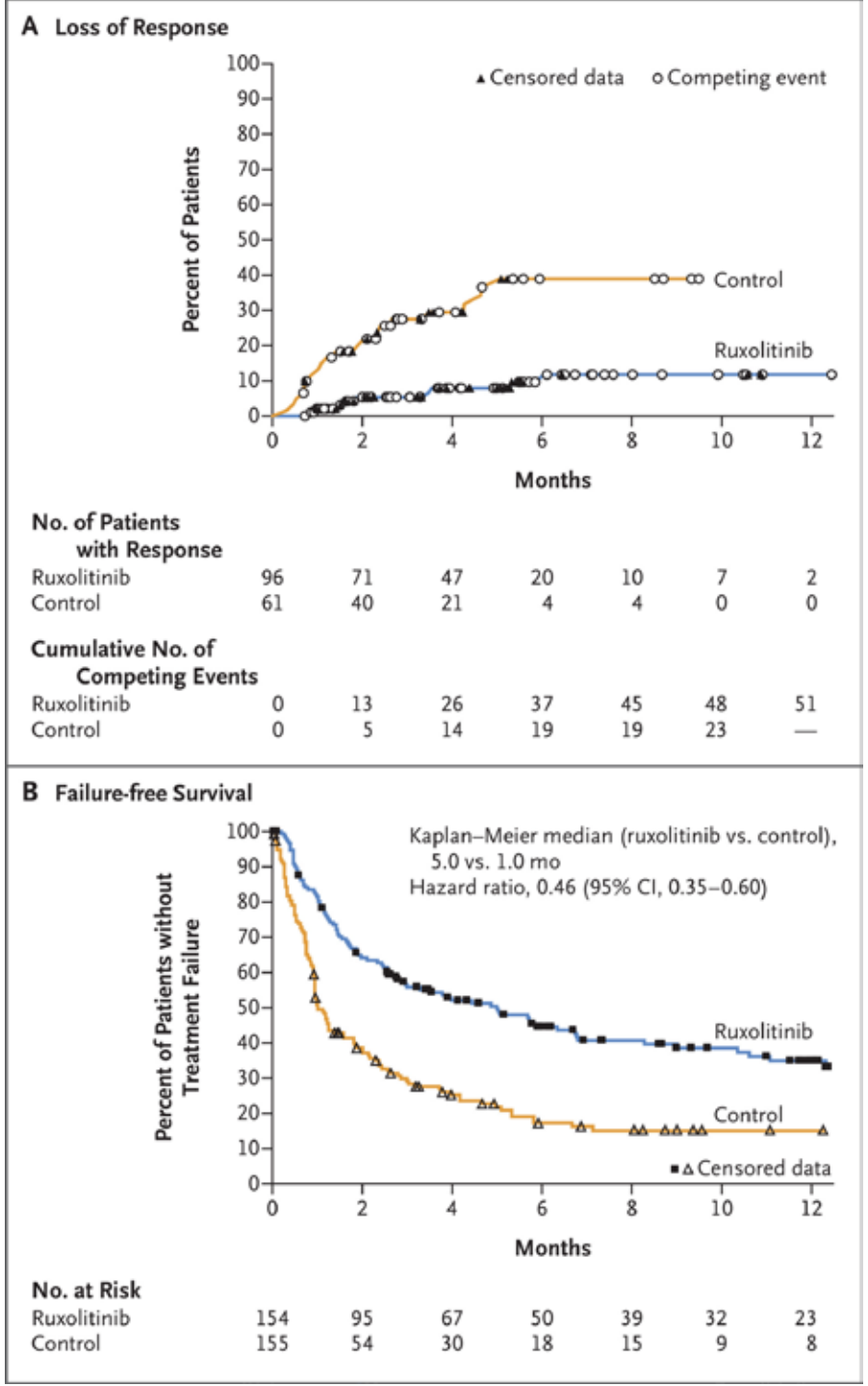
GVHD Staging			
Stage	Skin	Liver (total bilirubin)	GI tract (diarrhea output/day)
0	No GVHD rash	<2 mg/dl	Adult: <500 ml/d *Child: <10 ml/kg/d
1	Maculopapular rash <25% body surface area	2-3 mg/dl	Adult: 500-999 ml/d Child: 10-19.9 ml/kg/d -or- persistent nausea, vomiting, or anorexia with a positive upper GI biopsy
2	Maculopapular rash 25-50% BSA	3.1-6 mg/d	Adult: 1000-1500ml/d Child: 20-30 ml/kg/d
3	Maculopapular rash >50% BSA	6.1-15 mg/dl	Adult: >1500ml/d Child: >30 ml/kg/d
4	Generalized erythroderma (>50% BSA) plus bullous formation or desquamation >5% BSA	>15 mg/dl	Severe abdominal pain with or without ileus, or grossly bloody diarrhea
*Use adult values for patients ≥ 50 kg			
Overall Clinical Grade: Grade 0: No GVHD of any organ Grade 1: Stage 1-2 skin and no liver OR GI tract involvement Grade2: Stage 3 skin and/or stage 1 liver and/or stage 1 GI tract Grade 3: Stage 0-3 skin with stage 2-3 liver and/or stage 2-3 GI tract Grade 4: Stage 4 skin, liver, and/or GI tract			

Acute GVHD Treatment

- Standard Treatment is 2mg/kg of prednisone.
- 1mg/kg may be used for grade I-II aGVHD.
- Therapy given for 5-7 days prior to taper.
- Beclomethasone and Budesonide added for acute GVHD of upper and lower GI tract.
- 40-70% of patients are steroid responsive.
- No standard second line (Ruxolitinib)???
- Other options: ATG, ECP, MMF, Sirolimus, TNF inhibitors.

Reach-2 Trial of Ruxolitinib for Steroid Refractory GVHD





Zeiser R NEJM 2020

Chronic GVHD Characteristics

- As early as 50-60 days or as late as 400 days after transplant.
- 30-70% of patients
- Associated with increased TRM and decreased relapse.
- More frequent with:
  - Unrelated Donor Transplant
  - Peripheral blood
  - Older patients
  - Patients with history of acute GVHD

Chronic GVHD manifestations

- Oral and Ocular Sicca
- Serositis
- Fasciitis
- Esophageal and Vaginal Strictures
- Systemic Sclerosis
- Bronchiolitis Obliterans Syndrome

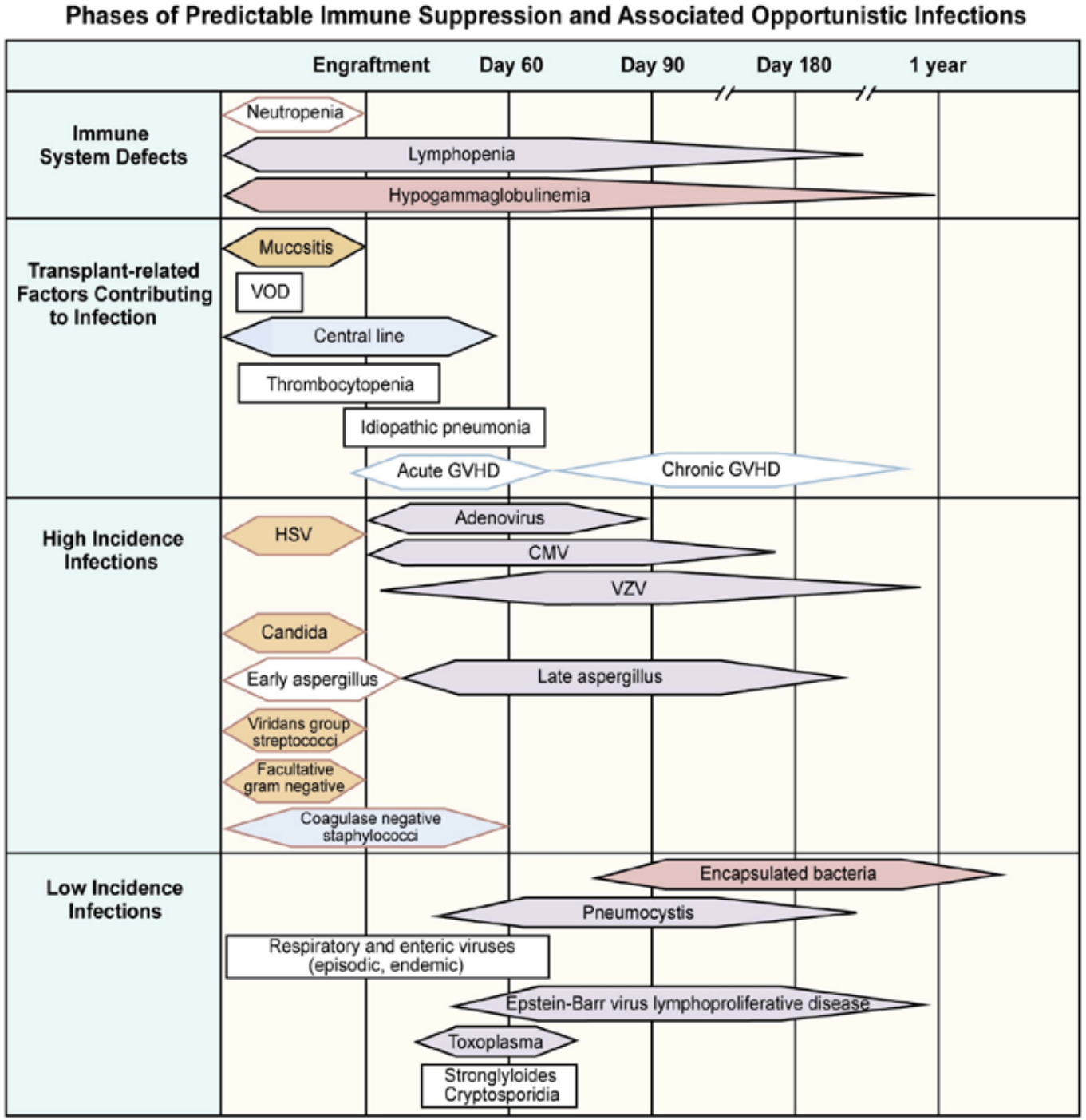
Bronchiolitis Obliterans Syndrome

- Bronchiolitis obliterans syndrome (BOS)
  - Non-productive cough
  - Progressive dyspnea
  - Obstructive changes on PFTs (FEV1/FVC < 70)
  - Air trapping on high res inspiratory/expiratory CT scan
  - Pathology: deposition of collagen and granulation tissue.
- Treat with FAM therapy (Fluticasone, Azithromycin and Montelukast)
  - Can prevent deterioration but rarely regain normal lung function

Chronic GVHD Treatment

- Mild
  - Oral-dexamethasone swishes
  - Ocular- preservative free artificial tears or CSA eye drops (Restasis)
- Moderate
  - Prednisone alone or in combination with a calcineurin inhibitor
  - Second line: Sirolimus, Ibrutinib, Ruxolitinib, ECP, clinical trial
- Average duration of therapy after PBSCT is 2-3 years.
- Increased risk of infections with encapsulated bacteria due to functional asplenia.
  - Prophylaxis with PCN VK

Infections


Phases of Predictable Immune Suppression and Associated Opportunistic Infections
Engraftment
Day 60
Day 90
Day 180
1 year
Immune System Defects
Neutropenia
Lymphopenia
Hypogammaglobulinemia
Transplant-related Factors Contributing to Infection
Mucositis
VOD
Central line
Thrombocytopenia
Idiopathic pneumonia
Acute GVHD
Chronic GVHD
High Incidence Infections
HSV
Adenovirus
CMV
VZV
Candida
Early aspergillus
Late aspergillus
Viridans group streptococci
Facultative gram negative
Coagulase negative staphylococci
Low Incidence Infections
Encapsulated bacteria
Pneumocystis
Respiratory and enteric viruses (episodic, endemic)
Epstein-Barr virus lymphoproliferative disease
Toxoplasma
Stronglyloides
Cryptosporidia

Infectious Prophylaxis

- Fungal
  - Fluconazole for patients at standard risk
  - Voriconazole or posaconazole for patients with prior fungal infection or pulmonary nodules on CT scan.
- Viral
  - Acyclovir or valacyclovir for reactivation of herpes simplex virus and varicella zoster
  - Letermovir for CMV
- PJP
  - Bactrim is first choice
  - Dapsone (check G6PD) (will not cover toxo)
  - Atovaquone
  - Inhaled pentamidine (will not cover toxo)

Early Infectious complications

- Neutropenic fever
  - Add Ceftazidime or Cefepime
  - If suspicion of gram positive-add Vancomycin
  - If Anaerobic due to intra-abdominal infection-add meropenem or metronidazole
  - Persistent fever > 72 hours consider antifungal therapy

CMV

- Patients who are CMV positive with CMV negative donors are most likely to reactivate.
- To prevent CMV disease, patients are started on letermovir
- Monitoring is done by PCR on a weekly basis.
- As soon as the virus is detected at a certain level of copies, ganciclovir or valgancyclovir is preemptively started.
- Foscarnet can also be used.

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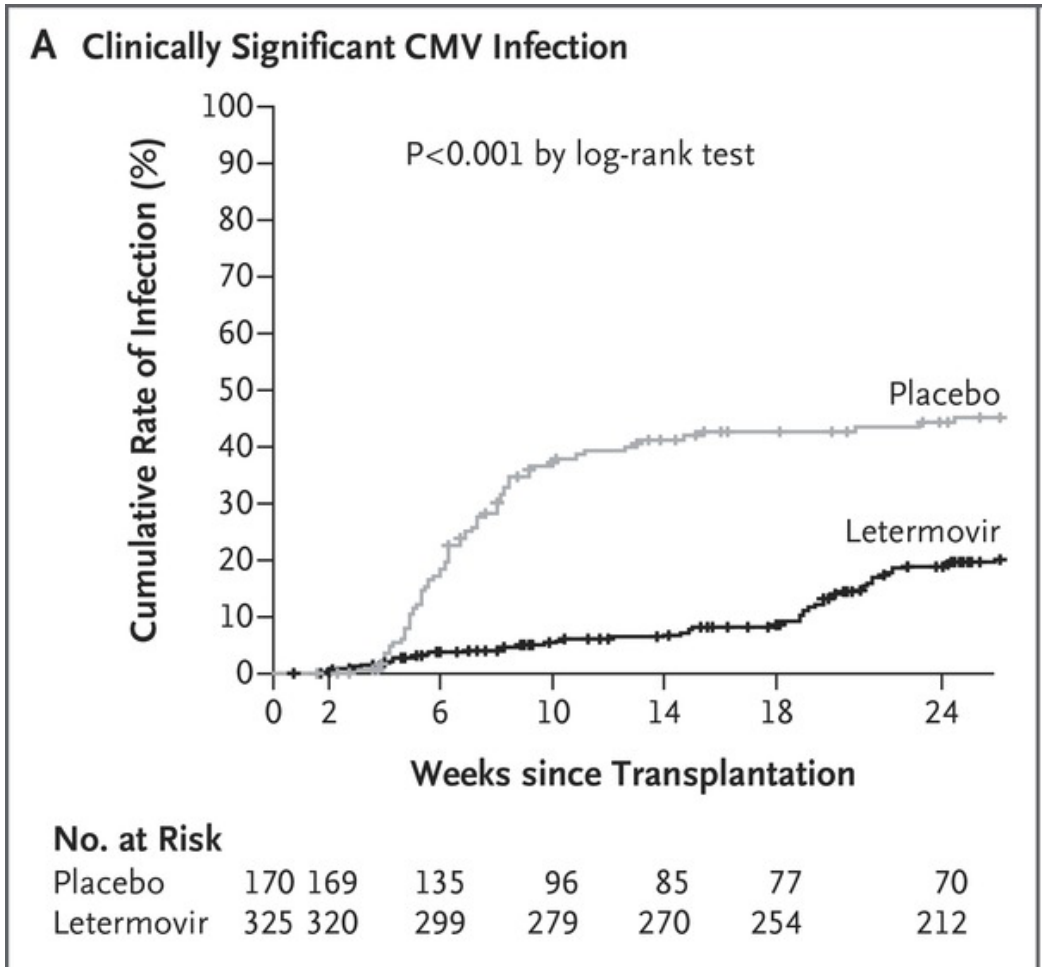

Marty FM et al NEJM 2017

Viral infections

- RSV, influenza, parainfluenza, metapneumovirus can cause upper or lower tract respiratory infections and can be life threatening.
- Patients with URI symptoms pretransplant should get NPT.
- Transplant is delayed for RSV, influenza or parainfluenza.
- Inhaled or oral ribavirin for parainfluenza and RSV.
- Tamiflu can shorten the course of influenza.

Fungal Infections

- Invasive candida should be considered in patients with neutropenia, mucositis or an indwelling catheter.
- Invasive aspergillus should be considered in patients with fevers, respiratory or sinus symptoms or new CNS or skin disease.
- Fungal disease should be confirmed by biopsy or BAL.
- Galactomannan often used in suspected aspergillus.
- Treatment is most frequently with voriconazole or posaconazole.
- Isavuconazonium (Cresemba) for resistant disease.

Late Effects

- 50% of long-term survivors report at least 1 late effect.
- Most common late effects:
  - Osteoporosis
  - Hypothyroid
  - Diabetes
  - Cataracts (10-20%)
  - Avascular Necrosis (10%)
  - Autoimmune disorder (3-5%)
- Among those living 5 years post HCT, there is 30% lower life expectancy than age matched controls.
- Leading cause of death of 5-year survivors: recurrent disease, secondary malignancy, chronic GVHD, respiratory ailments, and cardiovascular events.

Cryptogenic organizing pneumonia (COP)

- Can be seen both early and late.
- Characterized by fever, dry cough, shortness of breath.
- Chest imaging shows diffuse fluffy infiltrate.
- Pathology shows patchy fibrosis, granulation tissues and small airways.
- COP usually responds well to lengthy course of steroids (4-6 months) and is reversible (unlike BOS).

Secondary Malignancies

- Patients receiving high dose chemotherapy and radiation are at highest risk.
- Patients receiving T-cell depleted grafts are at higher risk of PTLD.
- Increase in solid tumors of 6-11% at 15 years.
- Incidence of MDS after Auto transplant can be as high as 10%.

Relapse after Auto Transplant

- Higher risk of relapse when performed after failure of initial chemotherapy.
- Patients who relapse after Auto may respond to conventional chemotherapy.
- RIC Allo-HCT has been found to be safe in those who relapse after Auto.
- Results are better in those with chemo-sensitive disease.

Relapse after Allo Transplant

- May have complete response with discontinuation of immune suppression
  - 25% response
  - 97% GVHD
- Donor Lymphocyte Infusion (DLI) can also result in complete remission
  - Response 60% with CML, 18% with ALL, 15% with AML
  - Patients with active disease should be reinduced prior to DLI
  - May result in GVHD (60%) of patients
  - Starting with low cell dose and increasing can lessen toxicity

Kekre et al Haematologica 2015; Dazzi et al Blood 2000

Newer treatments for relapse

- Chimeric Antigen receptor T-cells.
  - Most common in ALL.
  - Clinical trials for AML and Multiple Myeloma.
- Second Transplant
  - Younger patients
  - Patients who have at least a year interval from first transplant to relapse.
  - Controversial about whether it is beneficial to change donors.

Thank you and Questions???