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Overview of Hematopoietic Cell Transplantation

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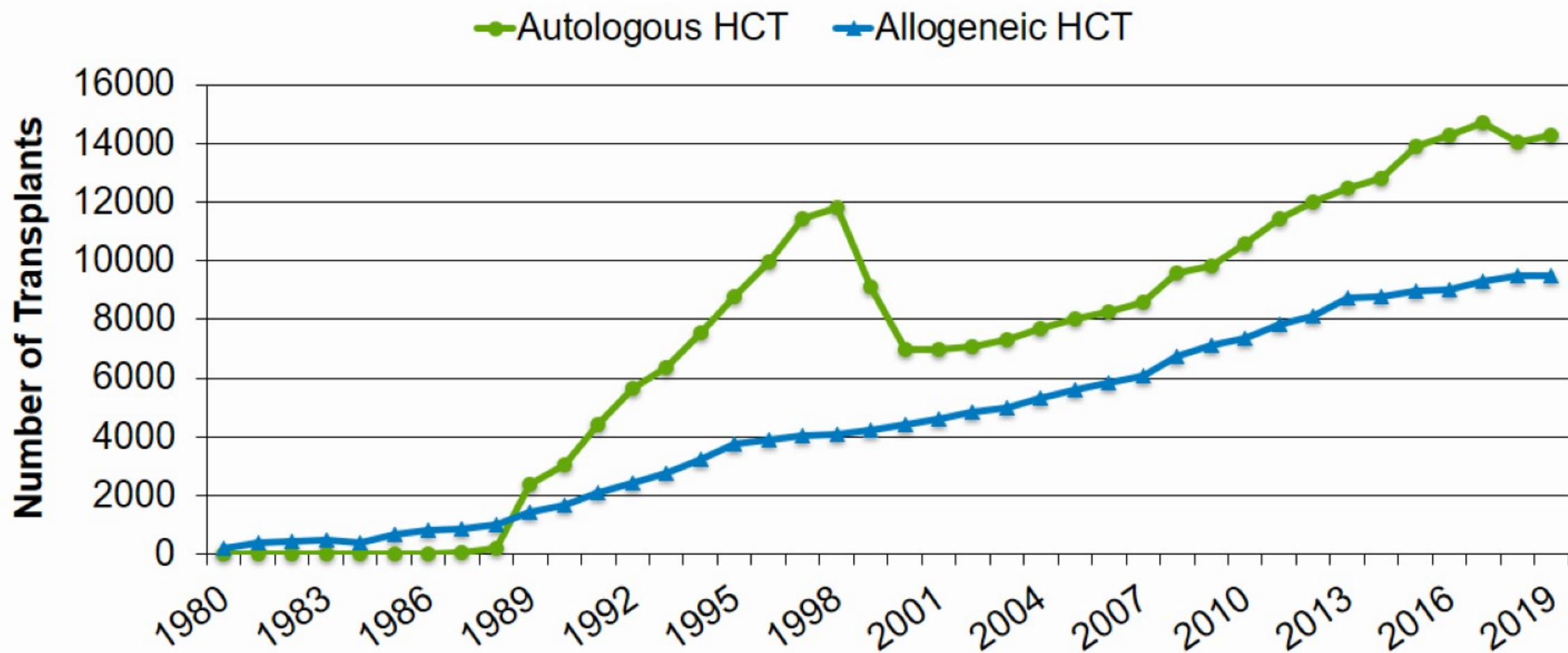
Outline

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

Graft Sources

- Autologous: from the patient
- Syngeneic: from an identical twin
- Allogeneic: from another person
 - Matched Sibling
 - Matched Unrelated Donor
 - Haploidentical (Half-matched Family Member)
 - Umbilical Cord Blood Unit (s)

Estimated Annual Number of HCT Recipients in the US by Transplant Type



Indications for Transplant

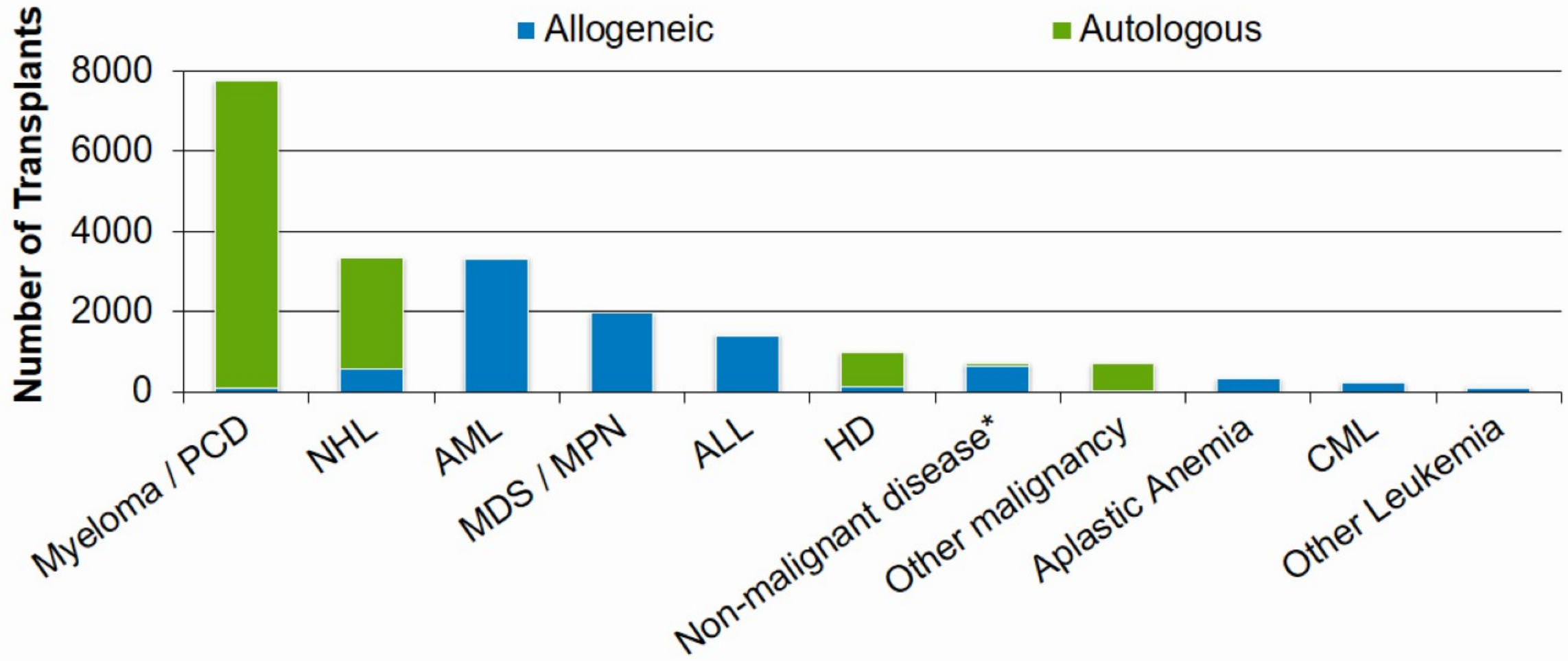
Malignant

- 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

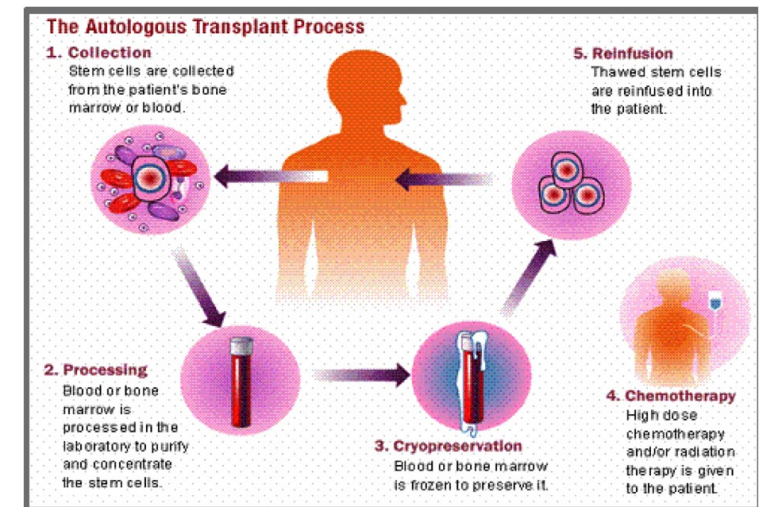
- Immunodeficiencies
- Aplastic Anemia
- Hemoglobinopathies
- Enzymatic Disorders
- Autoimmune Diseases

Indications for Hematopoietic Cell Transplant in the US, 2019



Autologous (Auto) Transplant

- Disease targeted myeloablative chemotherapy and followed by rescue with their own previously saved stem cells.
- Auto-stem cells are collected from G-CSF or chemo-mobilized peripheral blood.
- If the patient fails to mobilize, plerixafor may be administered
 - Plerixafor blocks the CXCR4-SDF-1a interaction, releasing stem cells from the bone marrow into the peripheral blood
- Frozen cells may be used more than 10 years later without change in CD34+ viability.
- Treatment-related mortality rate < 1%-3%.



Multiple Myeloma

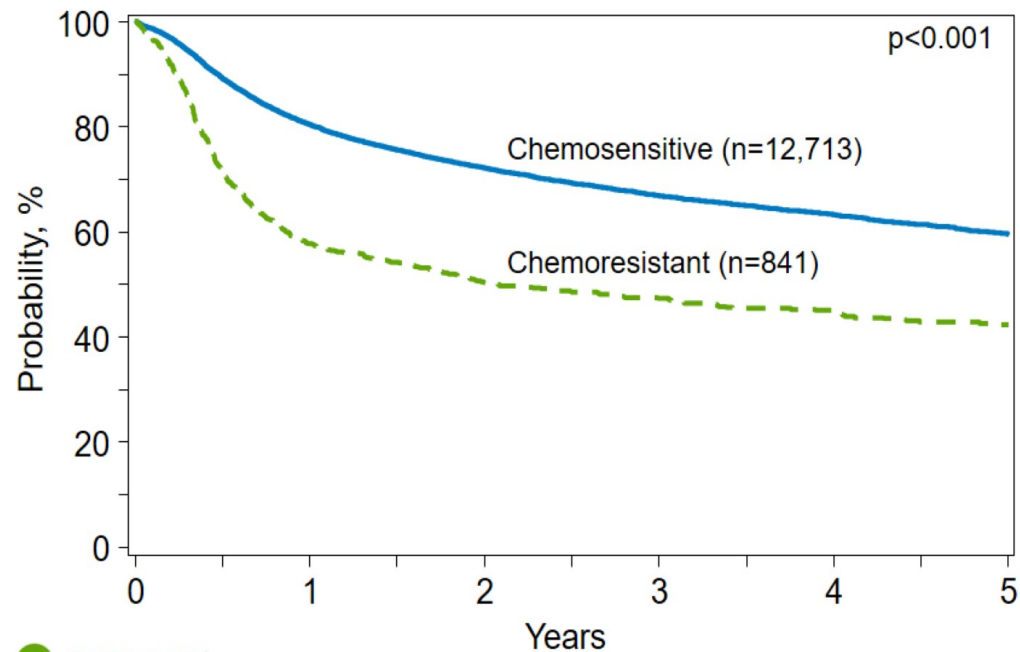
- Auto HCT improves survival in patients < 65 years old with newly diagnosed multiple myeloma.
- Progression free survival is longer if patients have HCT earlier rather than waiting for first relapse.
- Standard is Melphalan 200mg/m².
- PBSCT is more frequently used donor source.
- Maintenance with lenalidomide or bortezomib further improves PFS.
- 5-10% risk of post-HCT MDS depending on maintenance therapy.

Lymphoma

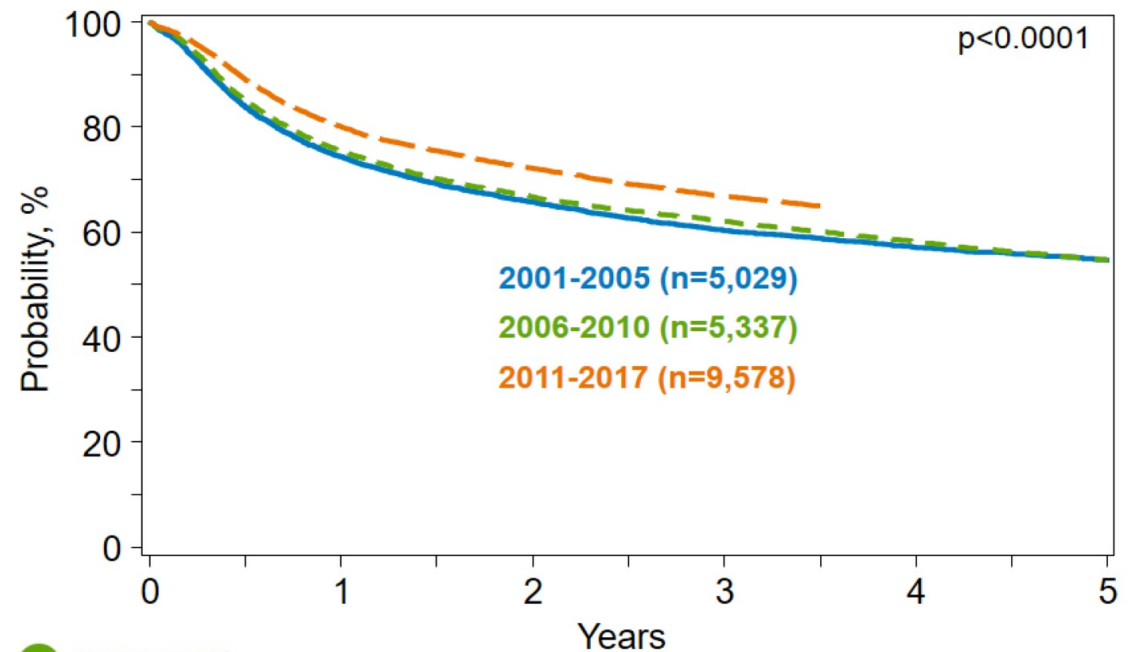
- Indications
 - Patients with primary refractory disease.
 - Never achieved remission
 - Remission < 6 months
 - Patients with relapsed disease.
- (R)-ICE or (R)-DHAP chemo-mobilization
- Standard is BEAM (BCNU, etoposide, cytarabine, and melphalan) chemotherapy
- Outcomes are better in patients with chemo-sensitive disease

Diffuse Large B-Cell Lymphoma

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

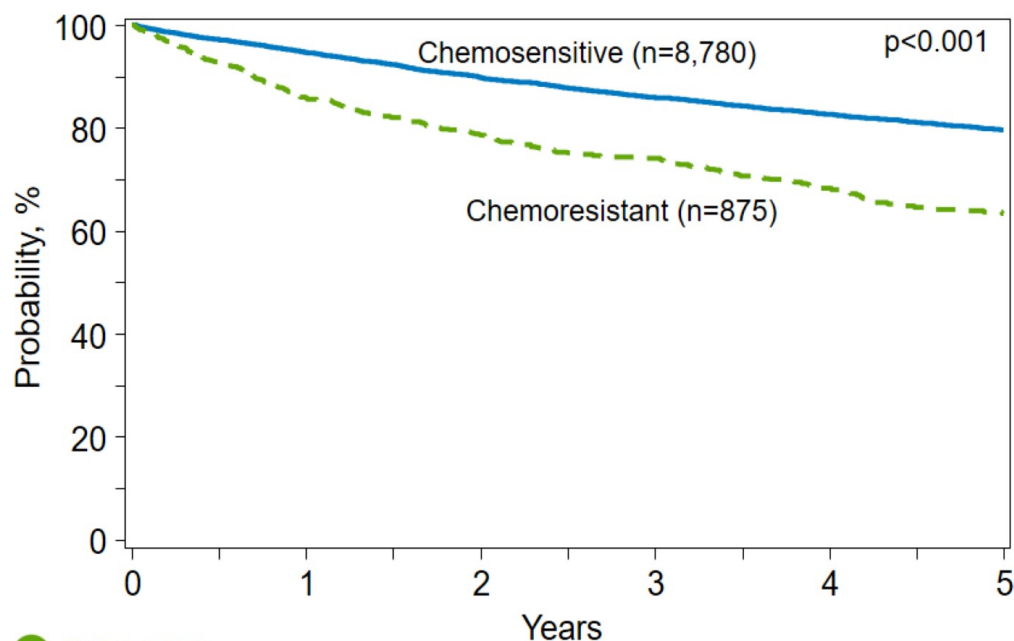


Trends in Survival after Autologous HCT for DLBCL, 2001-2017

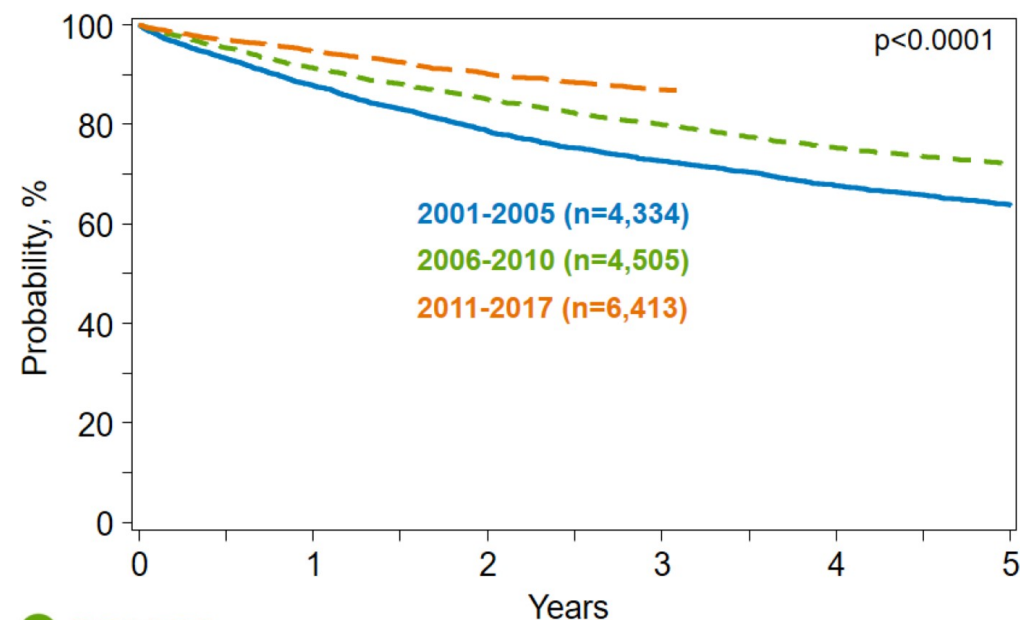


Hodgkin Lymphoma

Survival after Autologous HCT for Hodgkin Disease, 2007-2017

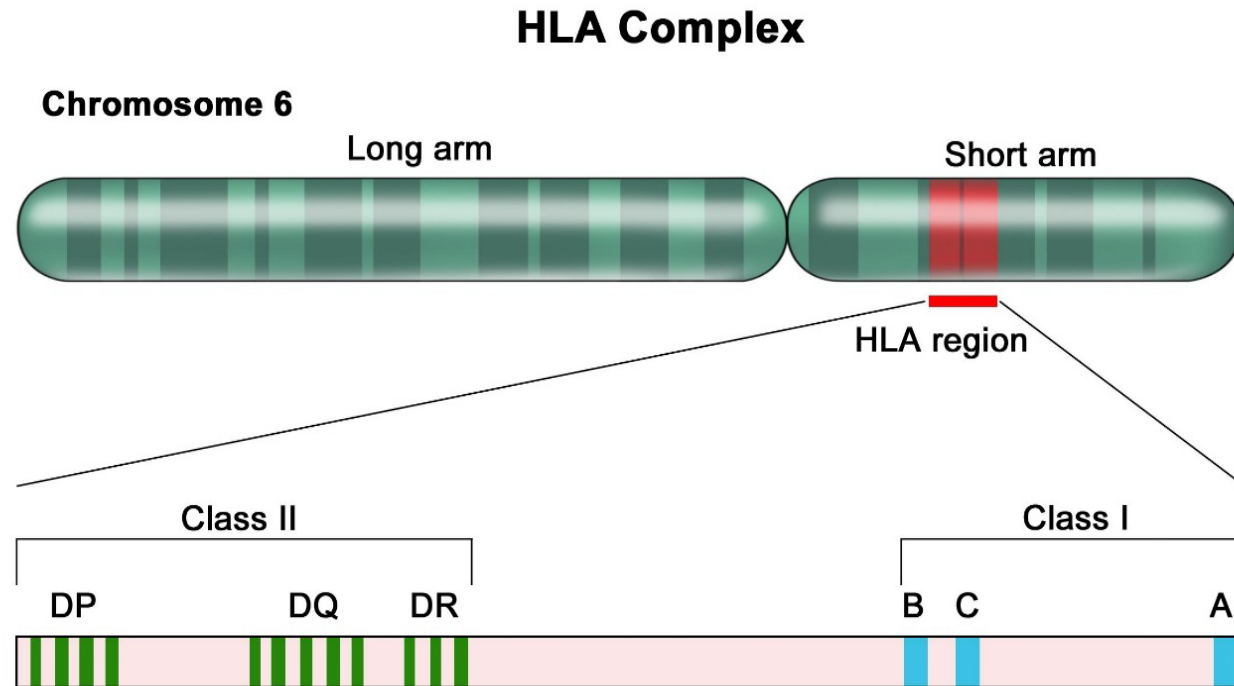


Trends in Survival after Autologous HCT for HD, 2001-2017



Allogeneic Transplant

- Utilizes both chemo/radiotherapy and graft versus tumor effect.
- HLA is encoded by the Major Histocompatibility Complex on chromosome 6.



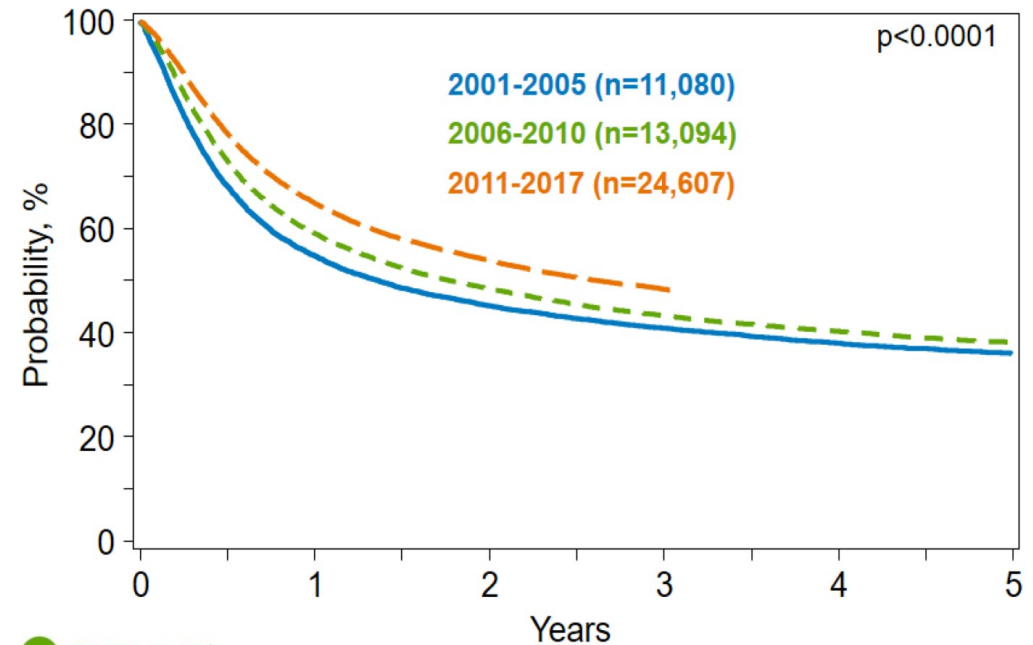
Donor search criteria

- 1:4 chance your sibling is a 10/10 match
- 1:2 chance your sibling is a Haplo match
- Unrelated Donor
 - Successful matching varies with ethnicity
- Search Criteria
 - HLA Match
 - Gender (male)
 - Age (younger)
 - CMV (-) for (-) recipient, (+) for (+) recipient
 - ABO matched (not necessary)

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.

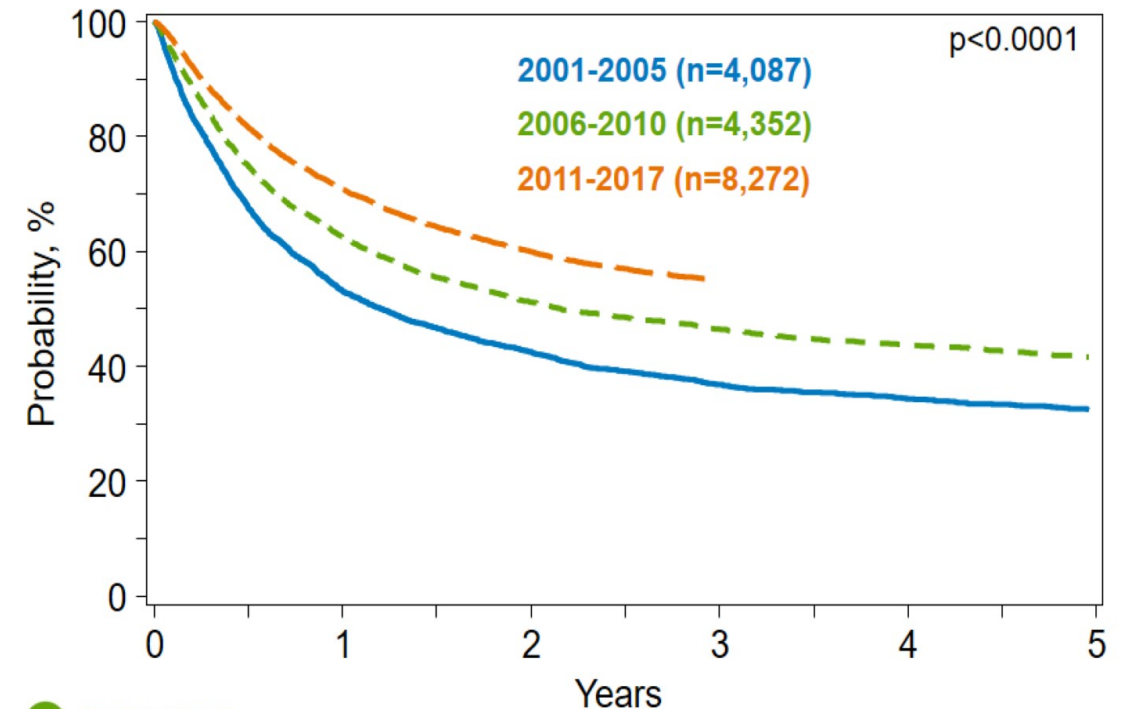
Trends in Survival after Allogeneic HCT for AML, ≥ 18 , 2001-2017



Allo HCT for ALL

- Long-term survival is improved with allo-HCT for patients with high-risk disease (MLL, 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.

Trends in Survival after Allogeneic HCT for ALL, ≥ 18 , 2001-2017



Allo-HCT for Myelodysplastic 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.

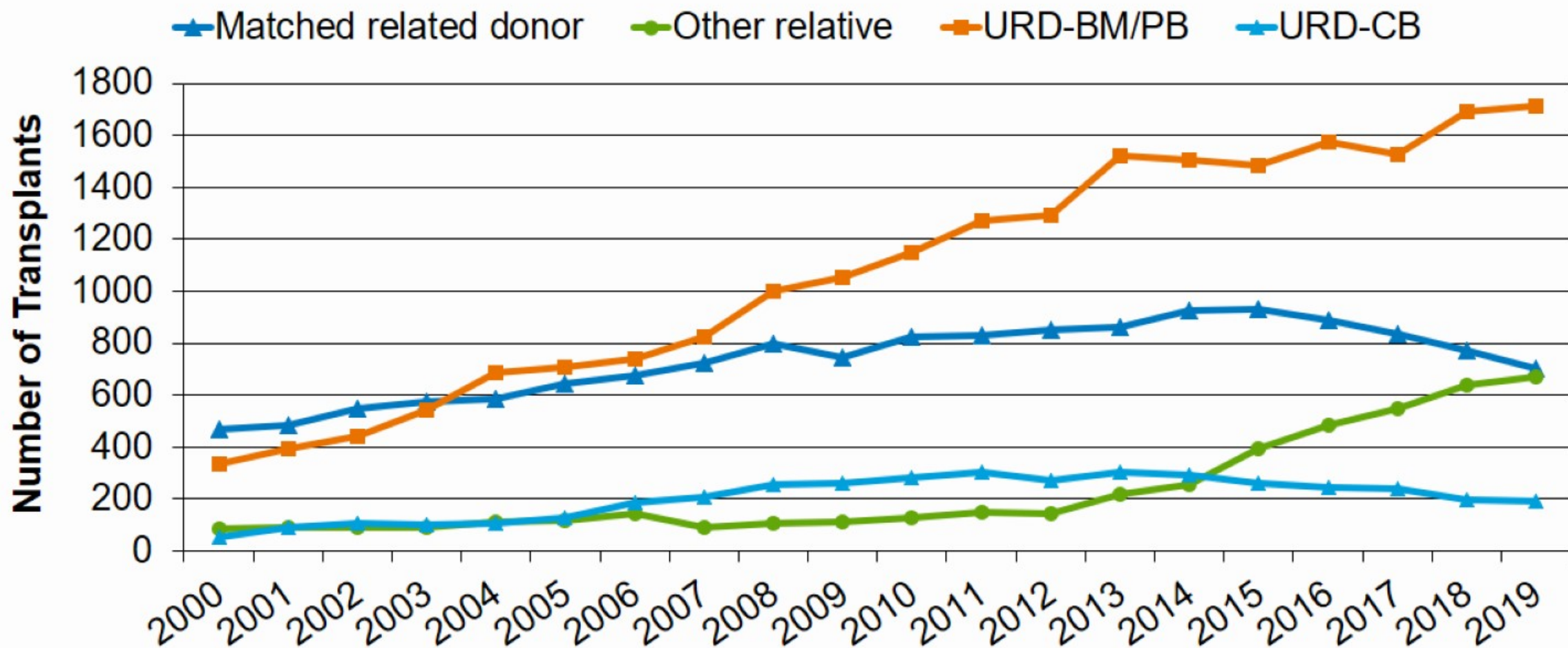


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Donor and Cell Sources

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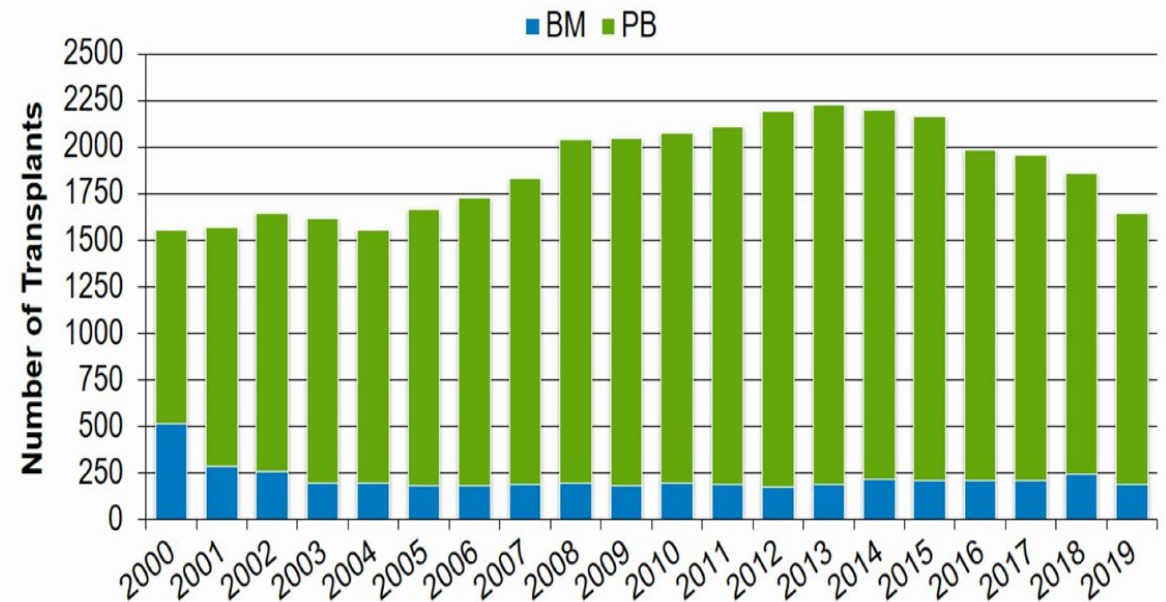
Trends in allogeneic HCT for Acute Myelogenous Leukemia (AML) by Donor Type in the US



Bone marrow (BM) vs PB (Peripheral Blood)

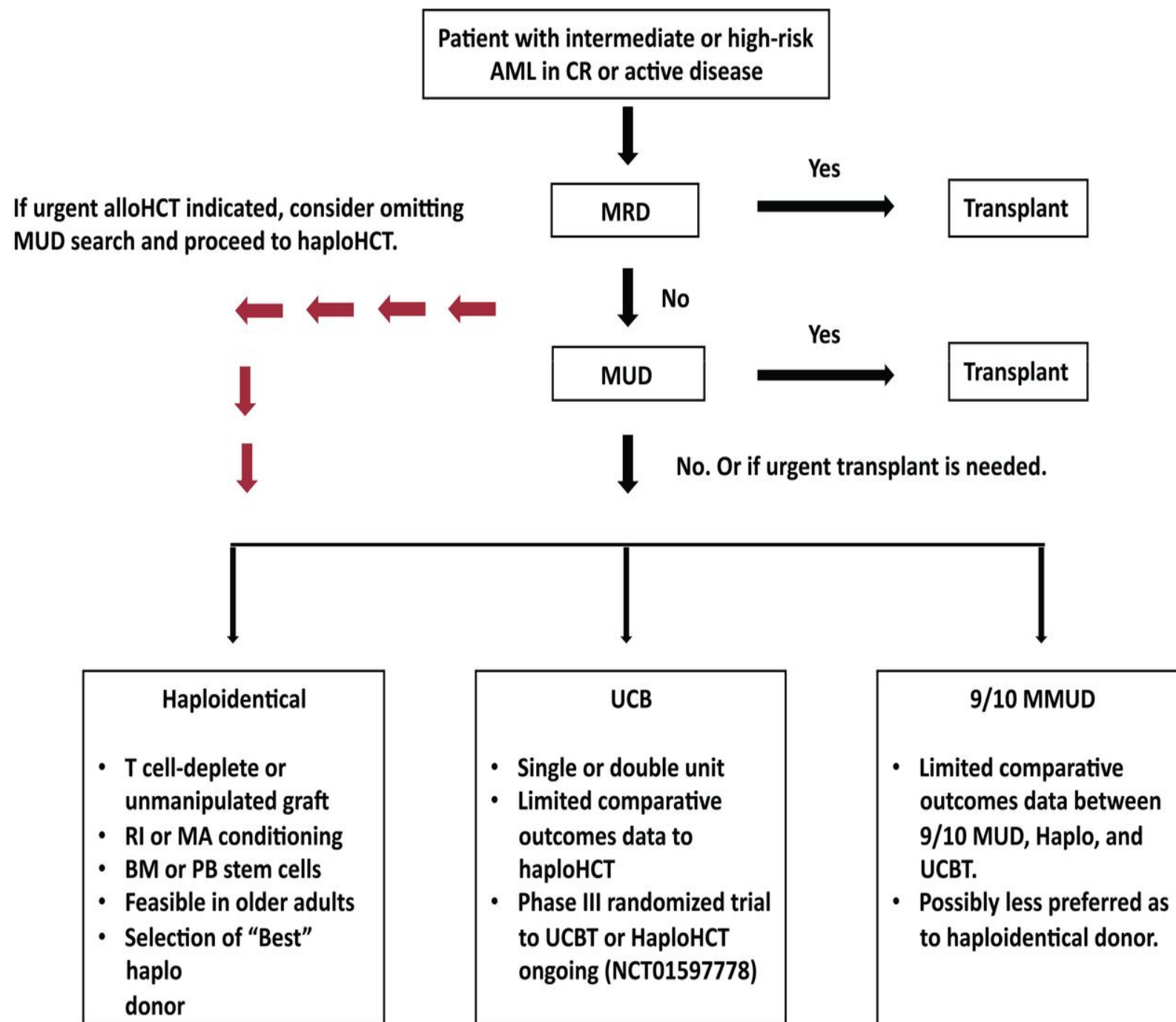
- Use of PB accelerates engraftment by about 7 days without increasing acute GVHD.
- PB has a higher proportion of T-cells than marrow.
- Chronic GVHD may be higher with PB than BM but disease recurrence appears to be less and survival equivalent

Matched Related Donor Allogeneic HCT in the US in Patients ≥ 18 Years



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.



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.

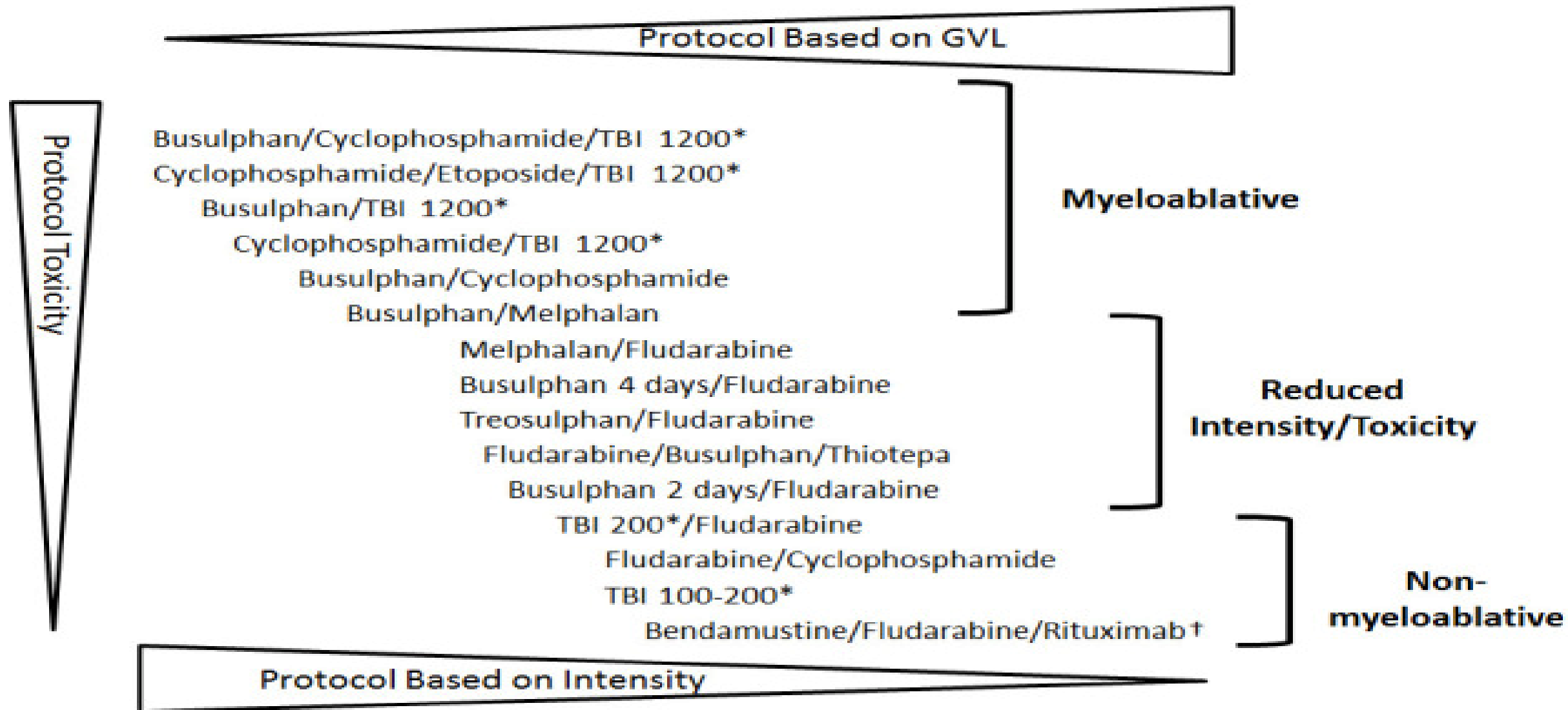
Haploidentical Donors

- 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.



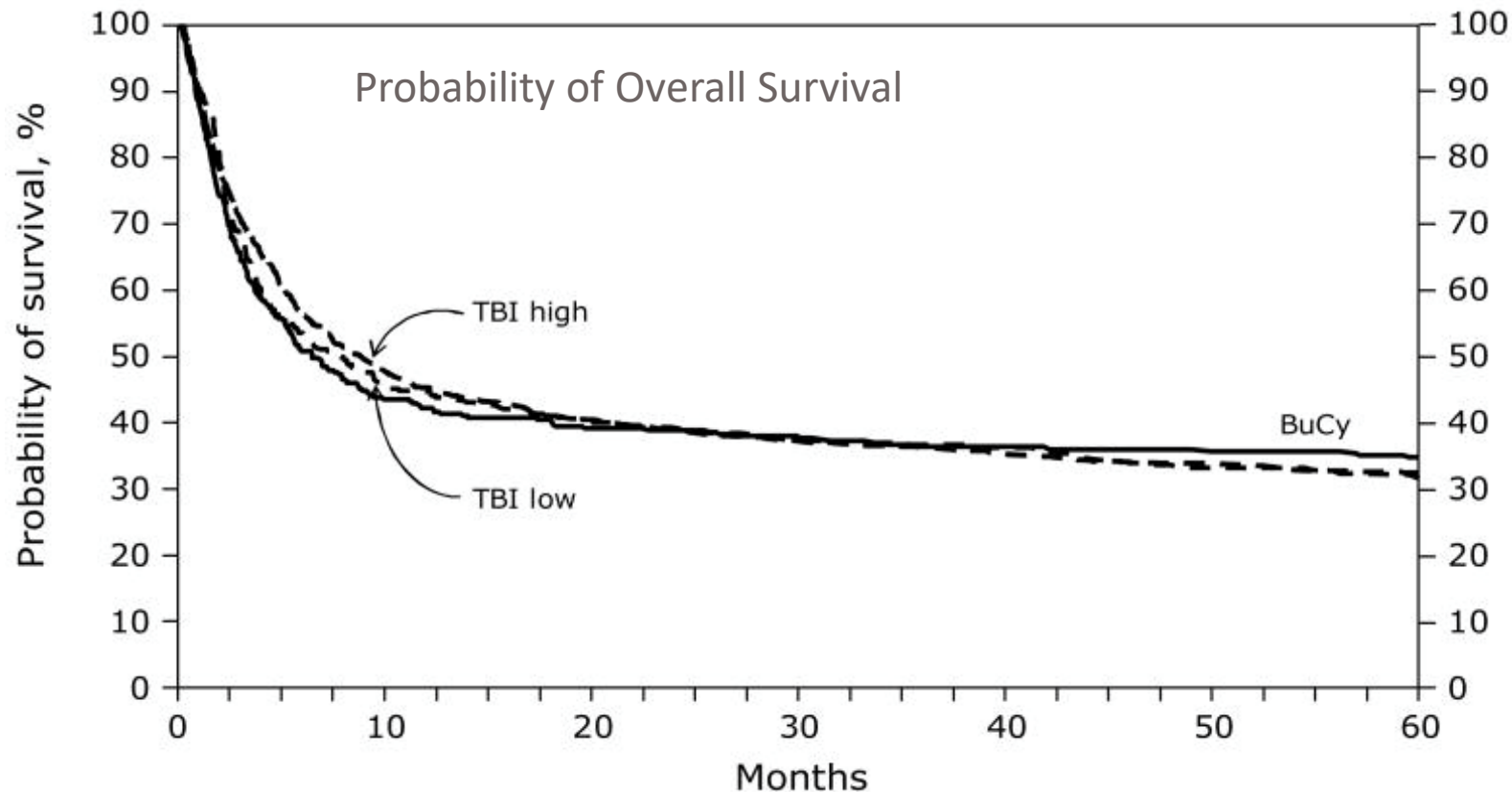
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Conditioning Regimens



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.



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

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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

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 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 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 \geq 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.

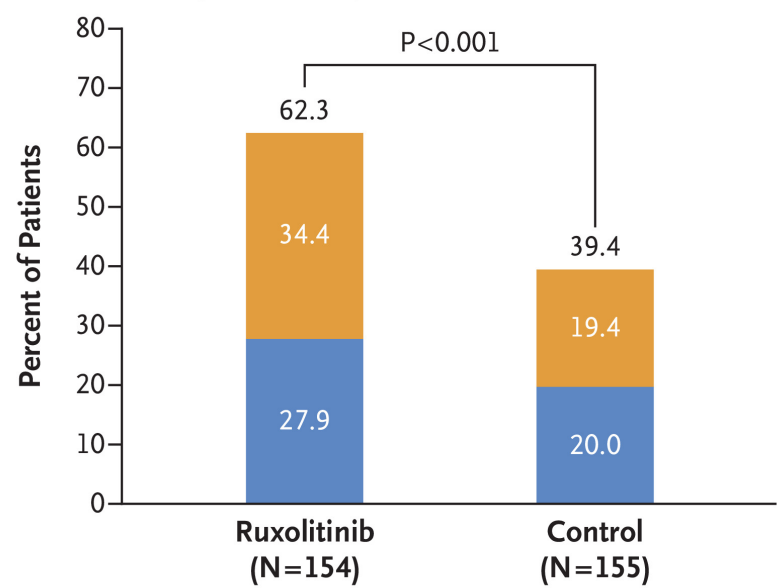
Reach-2 Trial of Ruxolitinib for Steroid Refractory GVHD

Zeiser R NEJM 2020

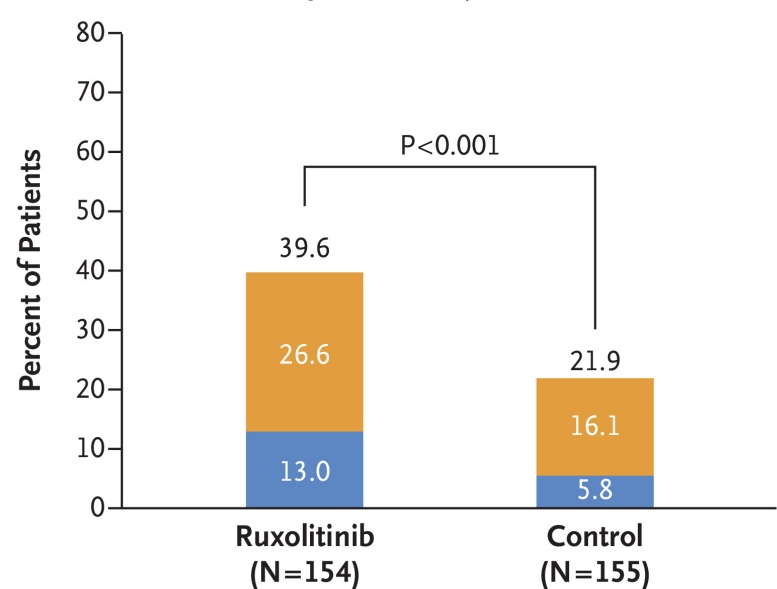
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Partial response Complete response

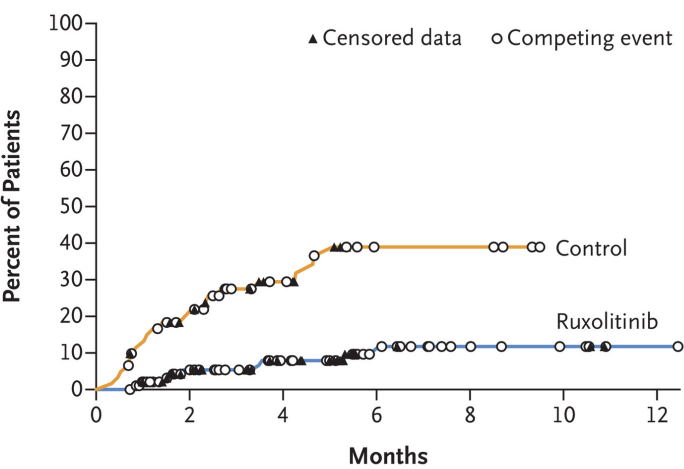
A Overall Response at Day 28



B Durable Overall Response at Day 56



A Loss of Response



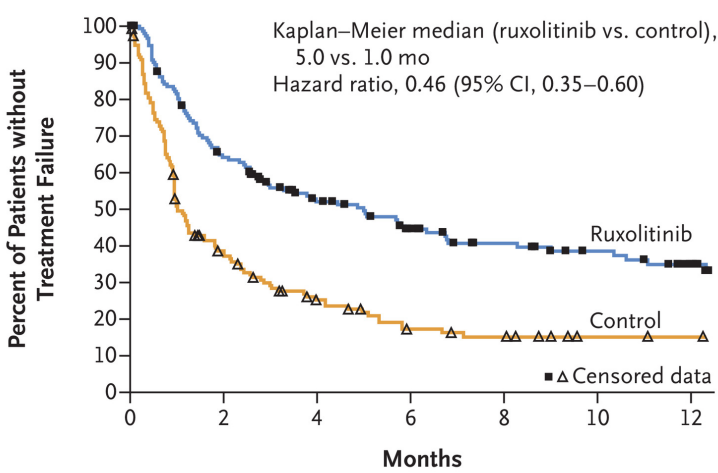
No. of Patients with Response

Ruxolitinib	96	71	47	20	10	7	2
Control	61	40	21	4	4	0	0

Cumulative No. of Competing Events

Ruxolitinib	0	13	26	37	45	48	51
Control	0	5	14	19	19	23	—

B Failure-free Survival



No. at Risk

Ruxolitinib	154	95	67	50	39	32	23
Control	155	54	30	18	15	9	8

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 ($FEV_1/FVC < 70$)
 - 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

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)

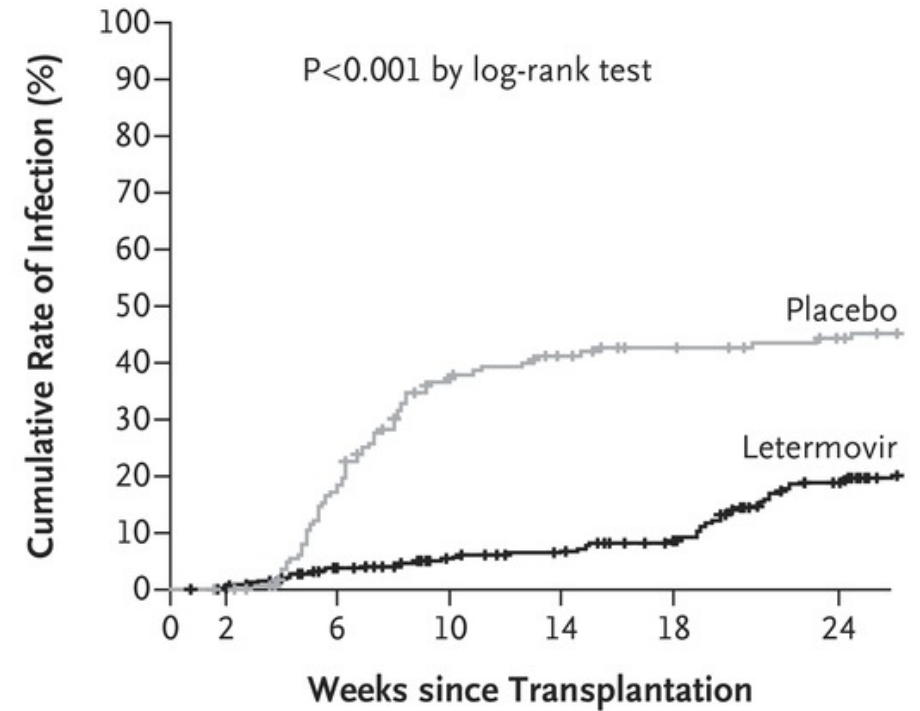
Early Infectious complications

- 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.

A Clinically Significant CMV Infection



No. at Risk

Placebo	170	169	135	96	85	77	70
Letermovir	325	320	299	279	270	254	212

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

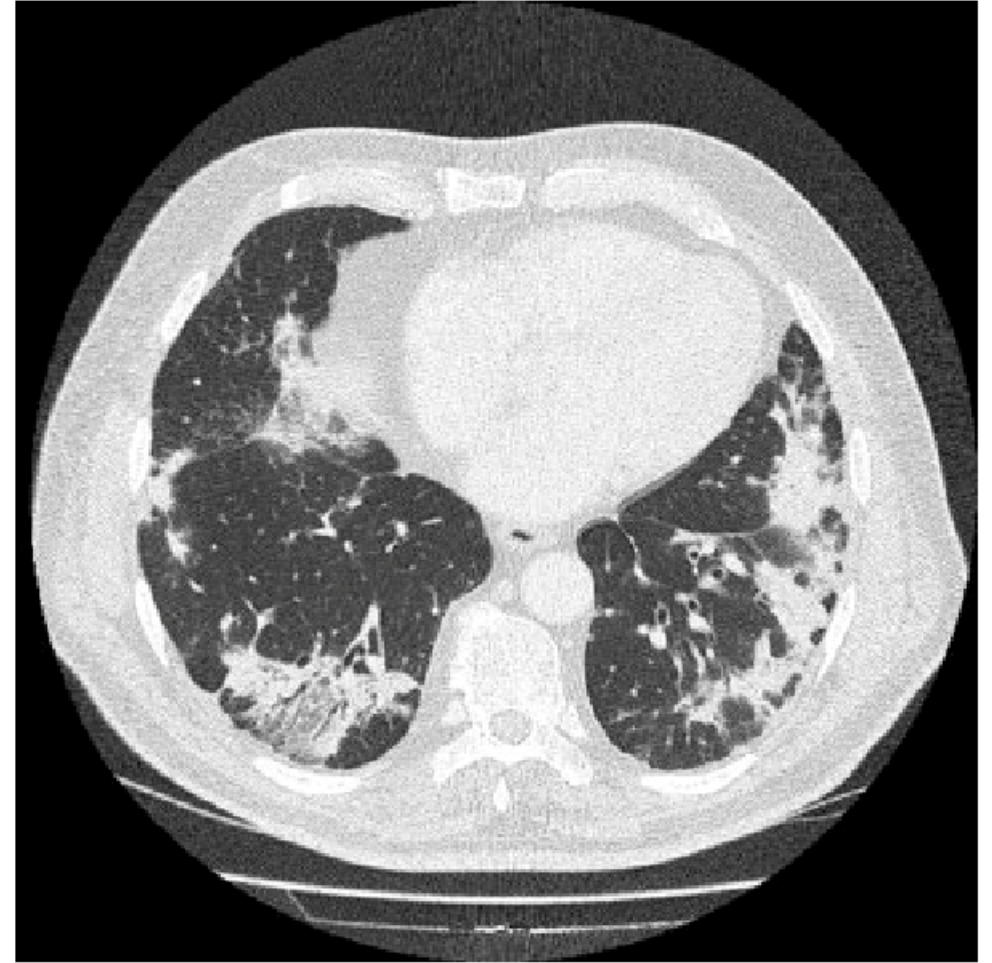
- Invasive candida should be considered in patients with neutropenia, mucositis or an indwelling catheter.
- Invasive aspergillus should be considered in patients with fevers, respiratory or sinus symptoms or new CNS or skin disease.
- Fungal disease should be confirmed by biopsy or BAL.
- Galactomannan 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

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???