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Managing Chronic Graft-Versus-Host Disease while living with ~~Leukemia~~

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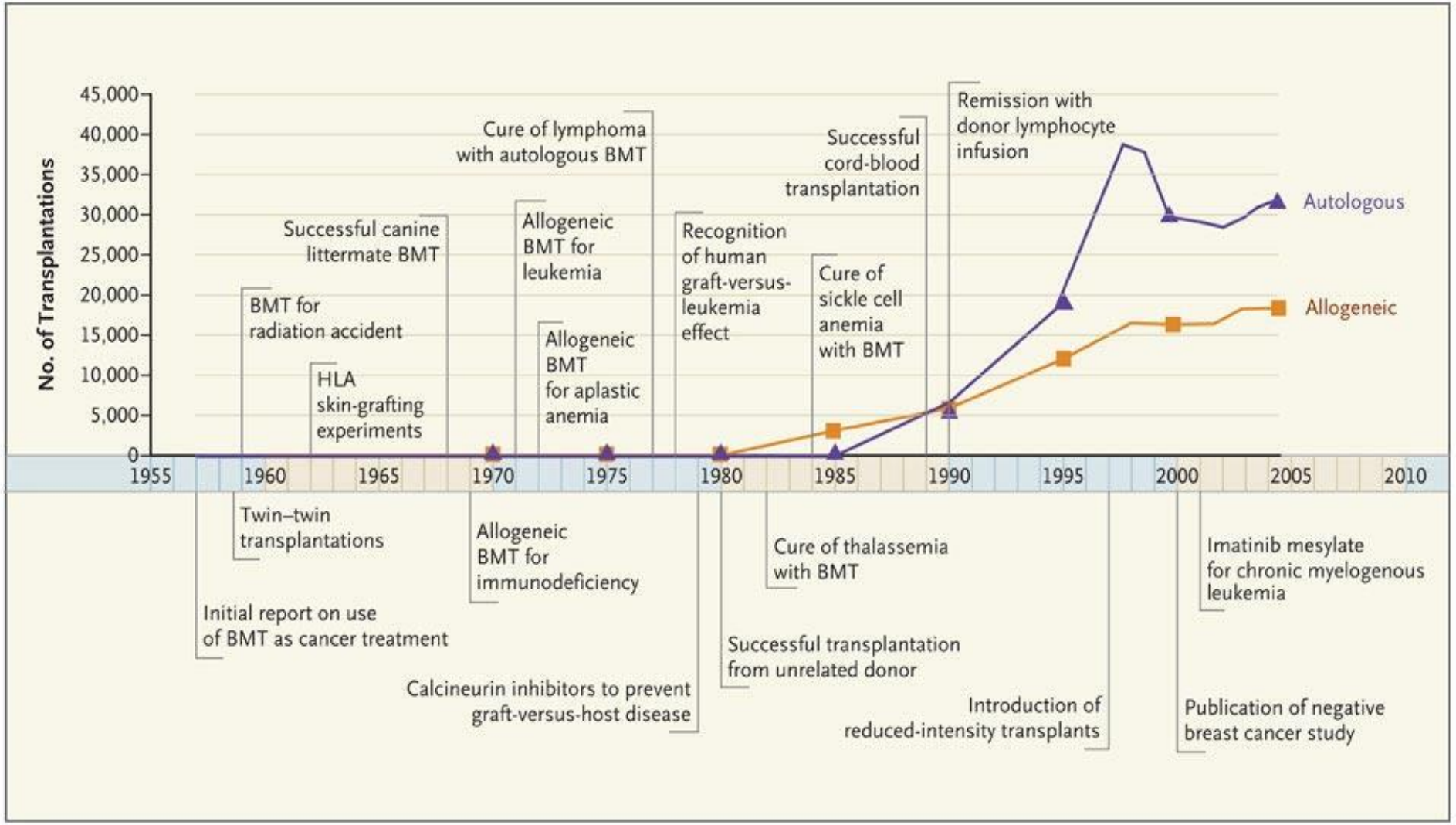
- No disclosures

Bone Marrow /Peripheral Blood Stem Cell Transplantations and Advances in the Field, 1957–2006



Appelbaum FR. N Engl J Med 2007;357:1472-1475.

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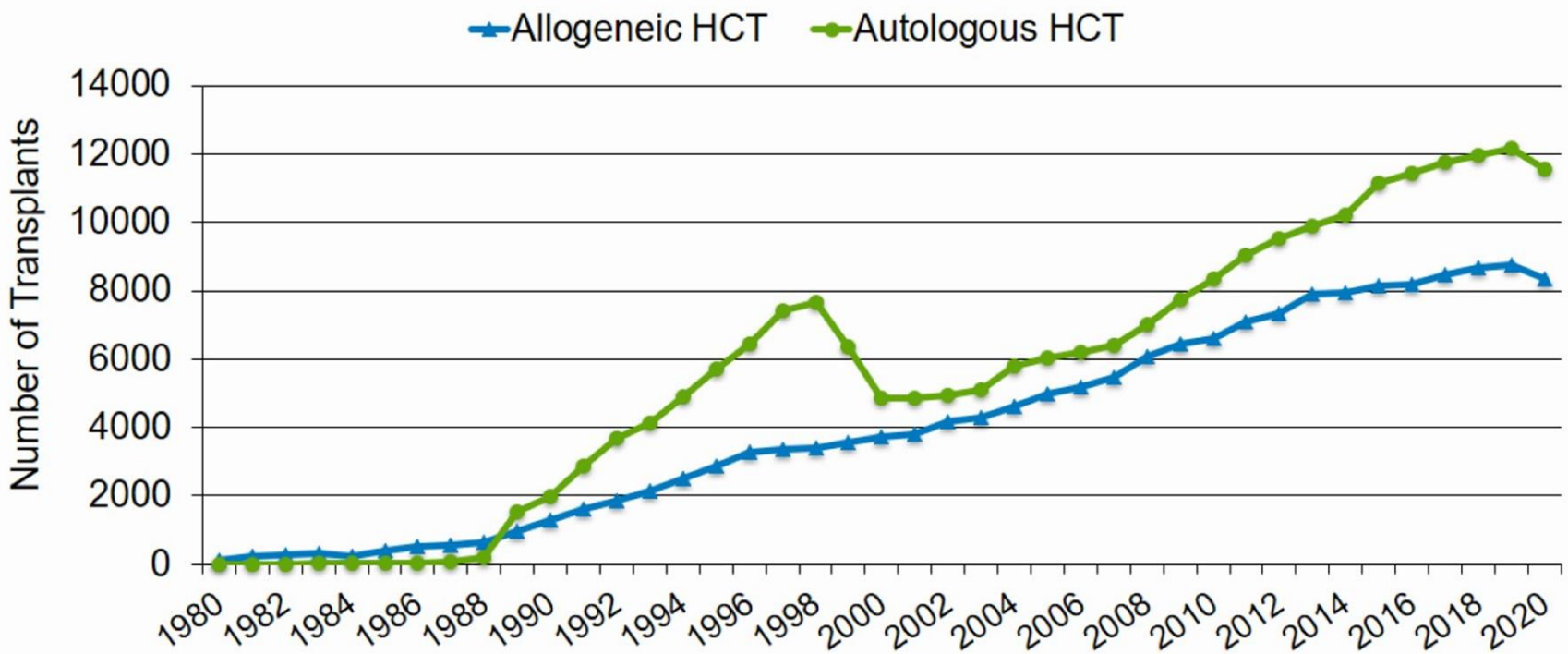
Number of HCTs in the US Reported to CIBMTR by Transplant Type



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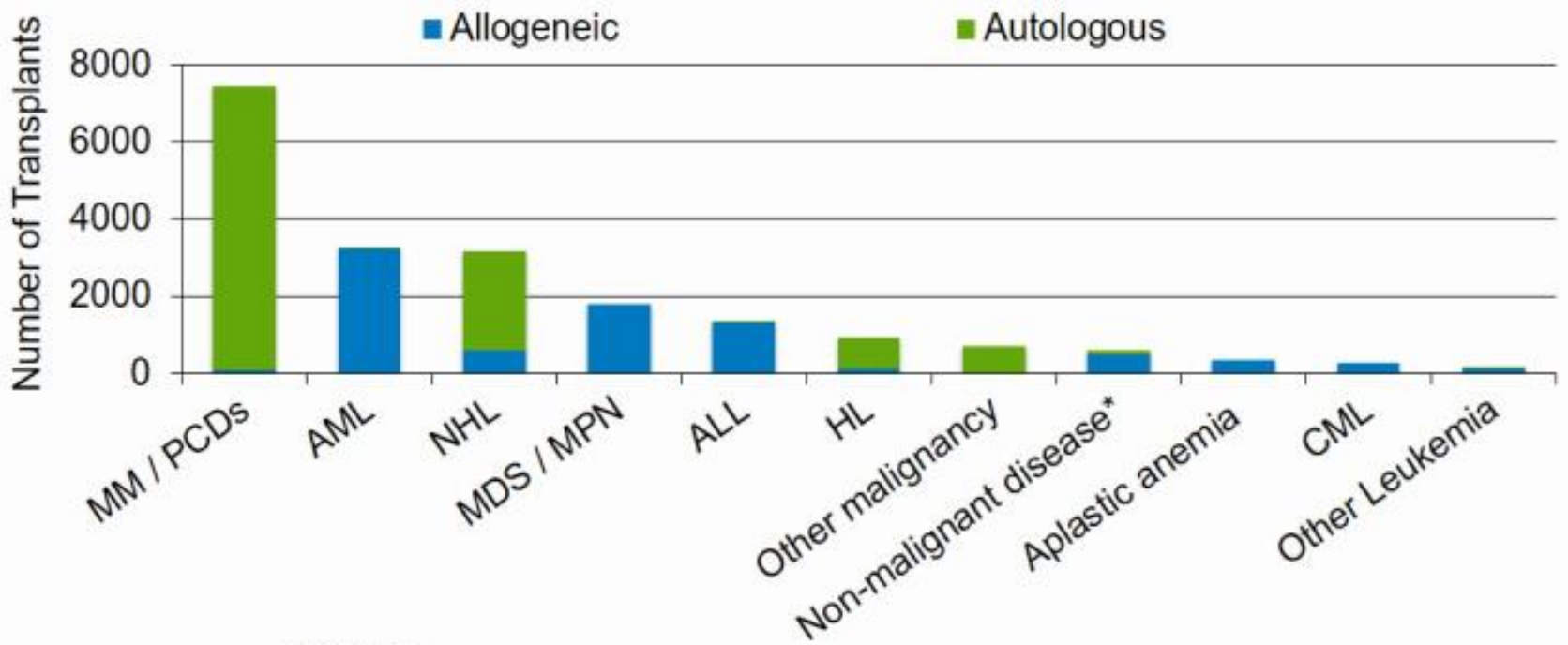
Number of HCTs by Indications in the US, 2020



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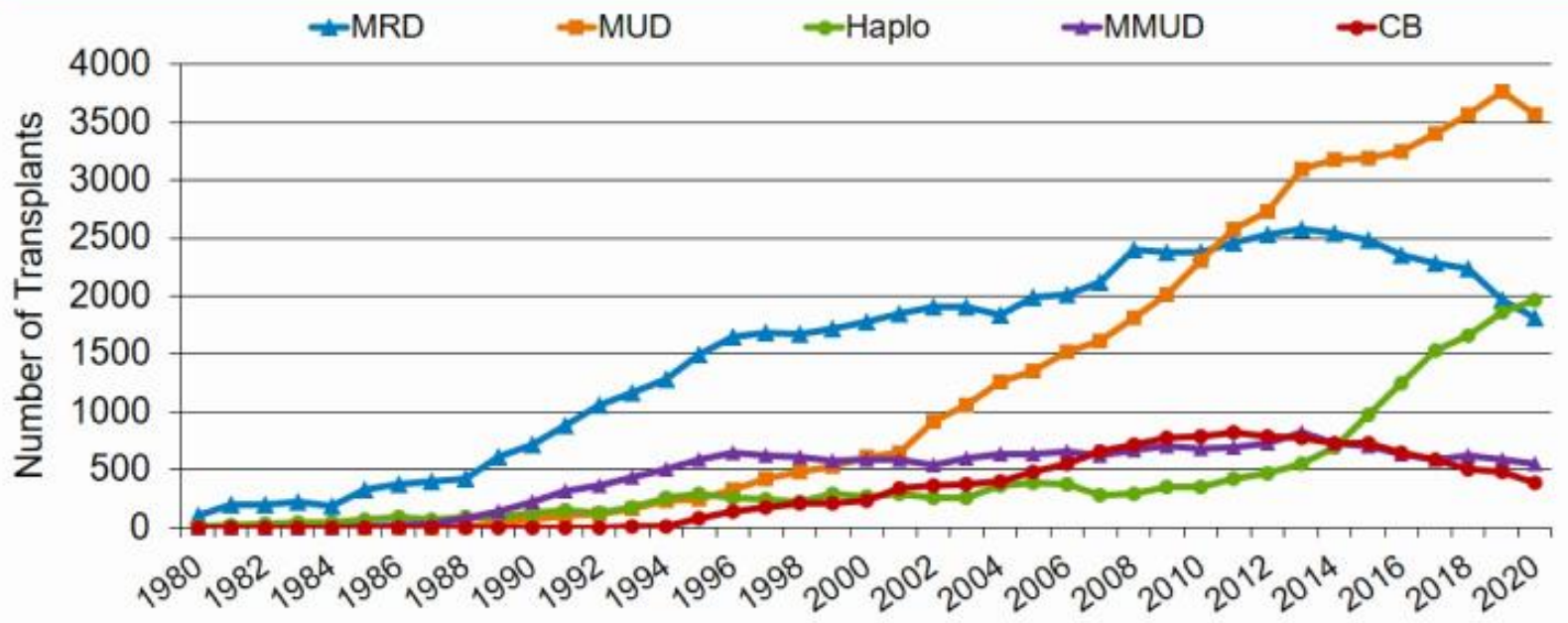
Abbreviations –
MM: Multiple myeloma;
PCDs: Plasma cell disorders;
AML: Acute myelogenous leukemia;
NHL: Non-Hodgkin lymphoma;
MDS: Myelodysplastic syndromes;
MPN: Myeloproliferative neoplasms;
ALL: Acute lymphoblastic leukemia;
HL: Hodgkin lymphoma;
CML: Chronic myeloid leukemia

*excludes Aplastic anemia

Number of Allogeneic HCTs in the US by Donor Type



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Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor;
Haplo: Haploidentical donor (includes all mismatched related donors); MMUD: Mismatched unrelated donor; CB: Cord blood

As of 2015……

Total **25,092,358 donors**

–24,489,329 unrelated donors

–603,029 CBU

•74 stem cell donor registries from 53 countries

•49 cord blood banks from 33 countries

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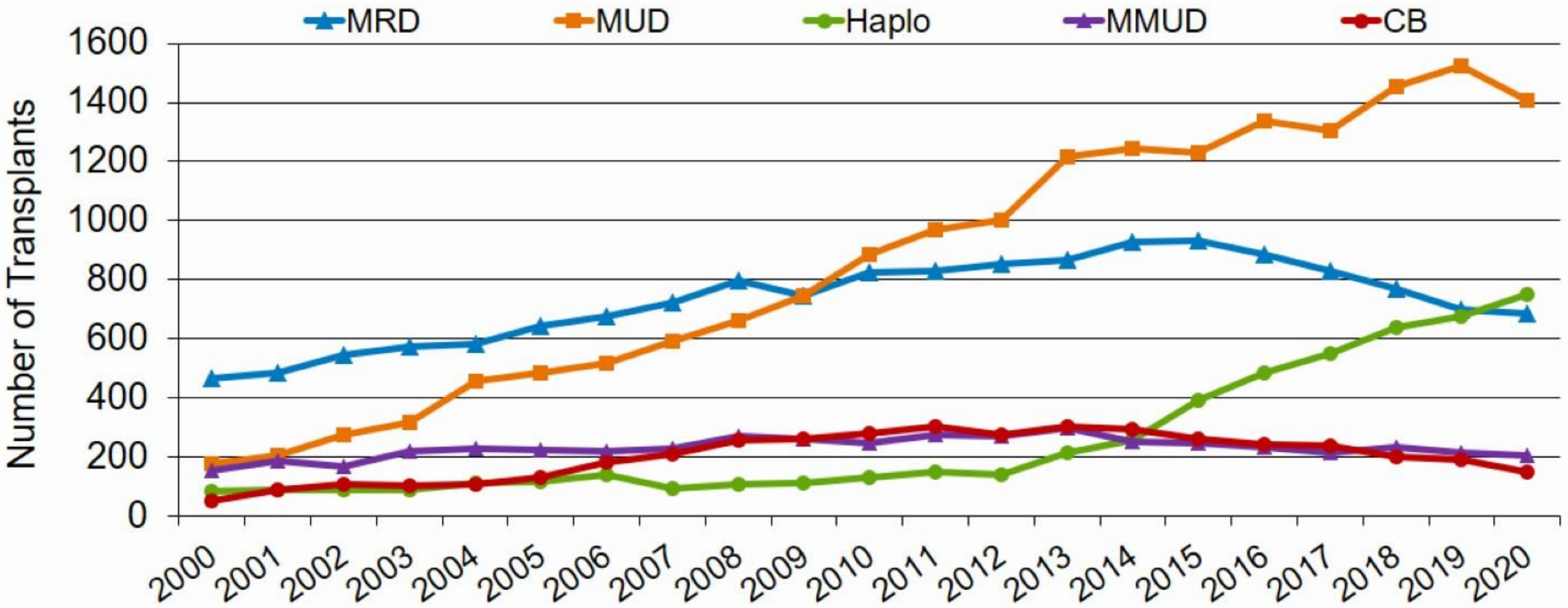
Number of Allogeneic HCTs for Acute Myelogenous Leukemia (AML) by Donor Type in the US



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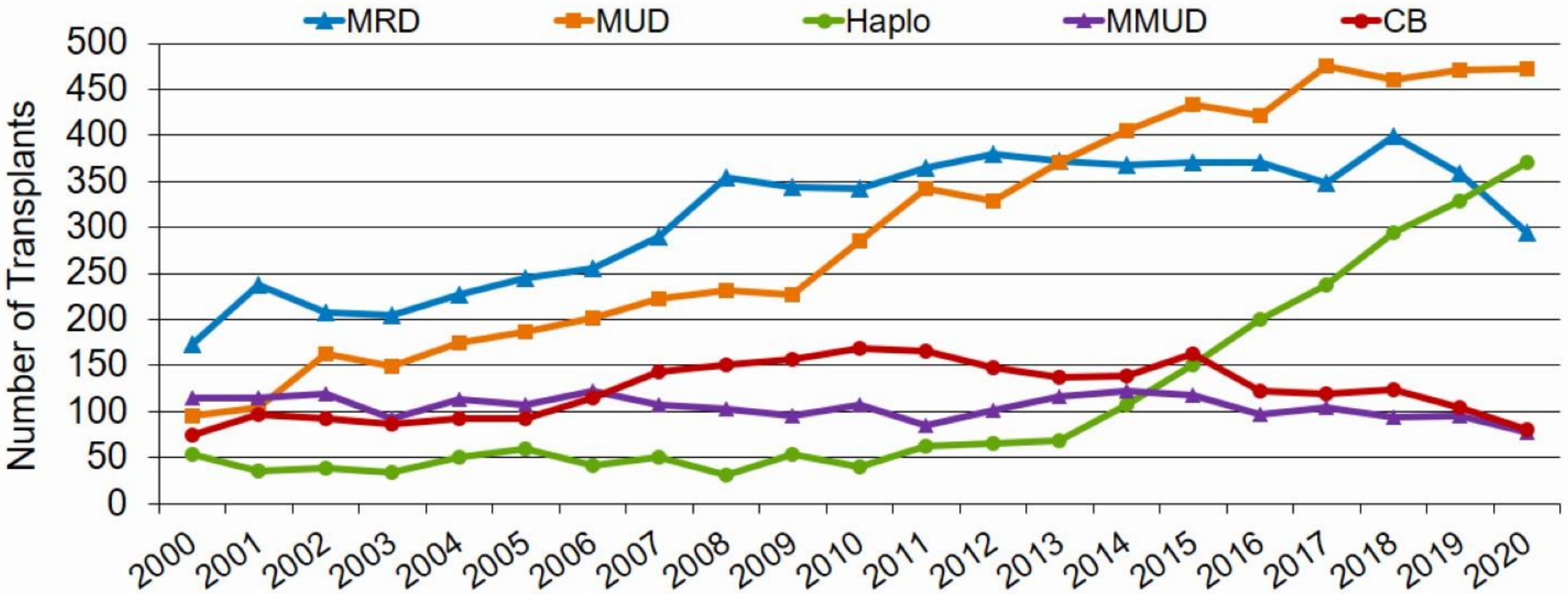
Number of Allogeneic HCTs for Acute Lymphoblastic Leukemia (ALL) by Donor Type in the US



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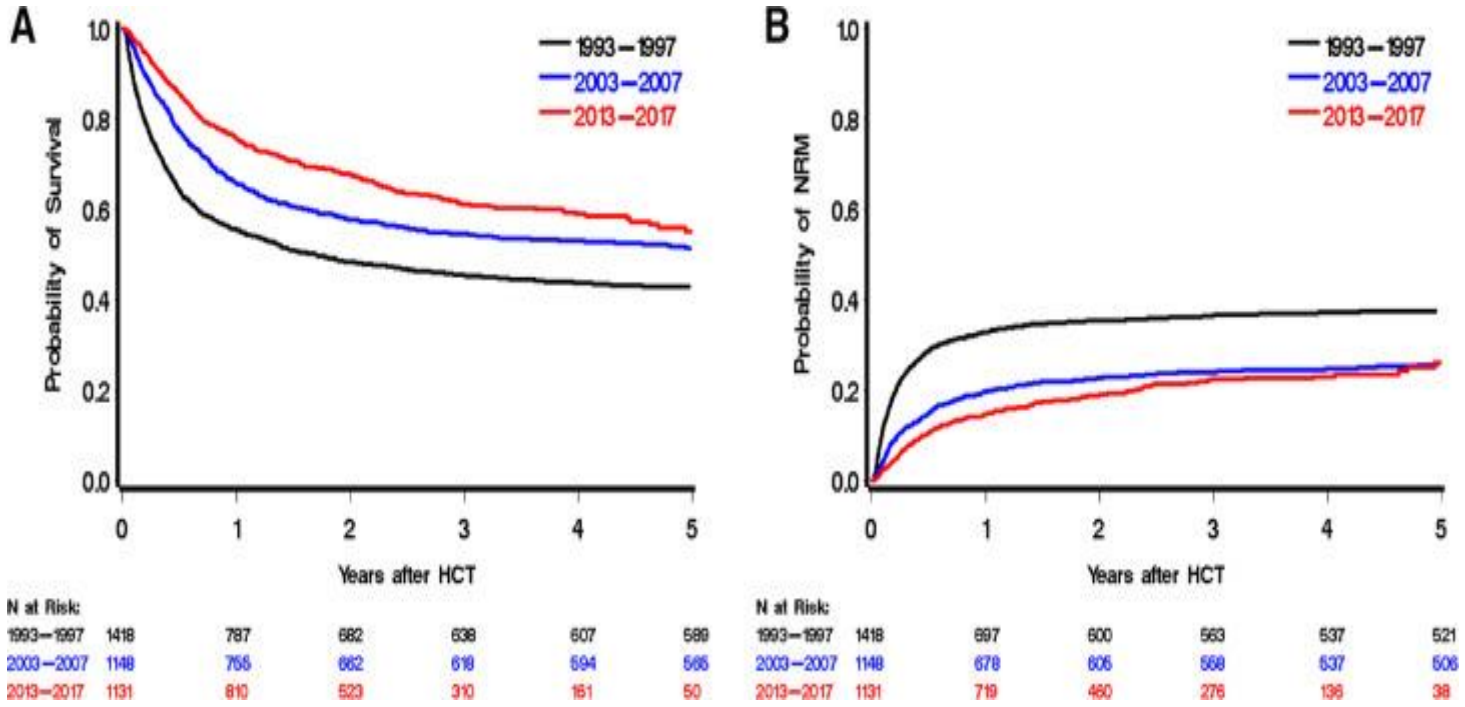
HSCT Survival and NRM over the years



Biol Blood Marrow Transplant 2020 Jul;26(7):1247-1256.

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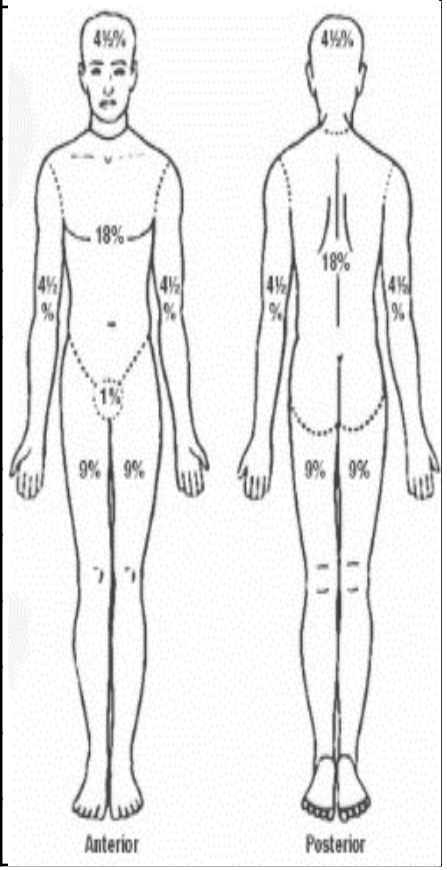
Graft Versus Host Disease

Acute GVHD

- Historically, occurs around the time of engraftment to day 100
- Classic aGVHD
- Persistent, recurrent or late aGVHD – occurs after day 100
- Incidence of 30% to 50% in MSD

Glucksberg Criteria

CLINICAL STAGING			
Stage	SKIN	LIVER (bilirubin)	GUT (output)
0	No rash	<2 mg/dL	<50ml/day or nausea or vomiting
I	Maculopapular rash, <25% BSA	2-3 mg/dL	500-999ml/day
II	Maculopapular rash, 25-50% BSA	3.1-6 mg/dL	1000-1500ml/day
III	Maculopapular rash, >50% BSA	6.1-15 mg/dL	>1500ml/day
IV	General erythema and bullous formation	>15 mg/dL	severe cramping +/- ileus
CLINICAL GRADING			
Grade	SKIN	LIVER	GUT
1	Stage I-II		
2	Stage III or	Stage I or	Stage I
3		Stage II-III or	Stage II-IV
4	Stage IV or	Stage IV	



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Chronic GVHD

- Multisystem immunologic disorder
- Chronic GVHD remains the leading cause of late morbidity and mortality
- Occurs in 30-70% of patient
- Starts later than aGVHD, about day 100 (oversimplification)

Chronic GVHD

- Mechanisms not well understood - ? induced by donor T cells, impaired T regulatory cell function, T and B cell homeostasis
- Can develop de novo, following resolution of GVHD, or as an extension of aGVHD
- Has some features of autoimmune disease

Risk factors for developing cGVHD

- Previous acute GVHD
- Age of recipient
- HLA mismatched donor/ unrelated donor
- Gender mismatched graft
- Parous female donor
- History of acute inflammation

Categories of GVHD

- Classic GVHD
- Overlap Syndrome

Early Recognition is key****

2014 Diagnosis and Staging Working Group

Table 1

Signs and symptoms of chronic GVHD

ORGAN OR SITE	DIAGNOSTIC (*Sufficient to establish the diagnosis of chronic GVHD*)	DISTINCTIVE* (*Seen in chronic GVHD, but insufficient alone to establish a diagnosis*)	OTHER FEATURES OR UNCLASSIFIED ENTITIES**	COMMON*** (*Seen with both acute and chronic GVHD*)
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric, affects most nails)		
Scalp and Body Hair		• New onset of scarring or non-scarring scalp alopecia, (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes), • Premature gray hair	
Mouth	• Lichen planus-like changes	• Xerostomia • Mucoceles • Mucosal atrophy • Ulcers • Pseudomembranes		• Gingivitis • Mucositis • Erythema • Pain
Eyes		• New onset dry, gritty, or painful eyes	• Photophobia • Periorbital hyperpigmentation	

Biol Blood Marrow Transplant. 2015 March ; 21(3): 389–401

ORGAN OR SITE	DIAGNOSTIC (*Sufficient to establish the diagnosis of chronic GVHD*)	DISTINCTIVE* (*Seen in chronic GVHD, but insufficient alone to establish a diagnosis*)	OTHER FEATURES OR UNCLASSIFIED ENTITIES**	COMMON*** (*Seen with both acute and chronic GVHD*)
		• Cicatricial conjunctivitis • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy	• Blepharitis (erythema of the eye lids with edema)	
Genitalia	• Lichen planus-like features • Lichen sclerosus-like features	• Erosions • Fissures • Ulcers		
Females	• Vaginal scarring or clitoral/ labial agglutination			
Males	• Phimosis or urethral/meatus scarring or stenosis			
GI Tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea • Vomiting • Diarrhea • Weight loss • Failure to thrive (infants and children
Liver				• Total bilirubin, alkaline phosphatase > 2 × upper limit of normal • ALT> 2× upper limit of normal
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy • Bronchiolitis obliterans syndrome (BOS)[‡]	• Air trapping and bronchiectasis on chest CT	• Cryptogenic organizing pneumonia (COP)[†] • Restrictive lung disease[†]	

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ORGAN OR SITE	DIAGNOSTIC (*Sufficient to establish the diagnosis of chronic GVHD*)	DISTINCTIVE* (*Seen in chronic GVHD, but insufficient alone to establish a diagnosis*)	OTHER FEATURES OR UNCLASSIFIED ENTITIES**	COMMON*** (*Seen with both acute and chronic GVHD*)
Muscles, Fascia, Joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis††	• Edema • Muscle cramps • Arthralgia or arthritis	
Hematopoietic and Immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (AIHA, ITP) • Raynaud's phenomenon	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

Biol Blood Marrow Transplant. 2015 March ; 21(3): 389–401

SITE SCORING				
	0	1	2	3
PS (KPS)	100%	80-90%	60-70%	<60%
Skin (BSA)	No sxs	<18% and no sclerotic features	19-50% or sclerotic	>50% or hidebound sclerotic or impaired mobility
Mouth	No sxs	No limitations	Partial limits on PO intake	Major limitation of PO intake
Eyes	No sxs	Not affecting ADL	Partially affecting ADL	Majorly affecting ADL
GI	No sxs	<5% wt loss	5-15% wt loss	>15% wt loss, or requiring esophageal dilation
Liver	Normal LFT (bili, AP, AST, ALT)	< 2x ULN	2-5x ULN	>5x ULN
Lungs	No sxs and FEV1 > 80%	FEV1 60-79%	FEV1 40-59%	FEV1 <39%
Joints & Fascia	No sxs	Mild tightness not affecting ADL	Tightness or contractures + mild/mod limitation of ADL	Contractures + decrease in ROM + limitation of ADL
Genital tract	No sxs	No effect on coitus or exam	Moderate signs on exam and mild dyspareunia	Advanced signs on exam and severe pain with coitus

OVERALL SCORE		
	Involved Sites	Max score
MILD	1-2	1
MODERATE	≥ 3	1
	1	2
	Lung	1
SEVERE	≥ 1	3
	Lung	≥ 2

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Severity of Disease Correlates with Survival

2 year overall survival

Mild cGVHD – 97%

Moderate cGVHD – 86%

Severe cGVHD – 62%

Goals of Treatment

- symptom burden reduction
- improvement of quality of life
- prevention of progression and inflammatory activity
- prevention of fibrosis and disability
- preservation of response to allow for withdrawal of immunosuppression
- repair and modulation of the immune system
- improvement of chronic GVHD

Hematology Am Soc Hematol Educ Program 2021 Dec 10;2021(1):648-654

Treatment

- Mainstay/1st line remains corticosteroids
- Ibrutinib

On August 2, 2017, the U.S. Food and Drug Administration approved ibrutinib (Imbruvica, Pharmacyclics LLC) for the treatment of adult patients with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. This is the first FDA-approved therapy for the treatment of cGVHD.

- Ruxolitinib

On September 22, 2021, the Food and Drug Administration approved ruxolitinib (Jakafi, Incyte Corp.) for chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

- Belumosudil

On July 16, 2021, the Food and Drug Administration approved belumosudil (Rezurock, Kadmon Pharmaceuticals, LLC), a kinase inhibitor, for adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

- Site-specific Treatment ****

More Treatments to Look Forward to….

- Itacitinib
- Abatacept
- Axalitinib
- Baricitinib
- Leflunomide
- Acalabrutinib
- Glasdegib
- Ofatumumab
- MSCs

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Hematology Am Soc Hematol Educ Program 2021 Dec 10;2021(1):648-654

Monitoring Post-Transplant

Tissue Organs	Complications	Procedure	Timing
Immune System	Infections	PCP prophylaxis Immunizations Endocarditis - AHA	For at least 6 month 6, 12 months, Annually As recommended
Ocular	Cataracts Sicca Syndrome	Ophthalmologic examination	6, 12 months, Annually
Oral	Sicca Syndrome Caries/Periodontal disease Oral Cancer	Dental Assessment	6, 12 months, Annually
Respiratory	IPS COP BOOP Sino-pulmonary ifx	PFTs Radiologic studies	6, 12 months, Annually /Depending on symptoms

* Frequency affected by presence of GVHD, being on steroids, use of TBI

Monitoring Post-Transplant

Tissue Organs	Complications	Procedure	Timing
Cardiovascular	Cardiomyopathy CHF CAD PAD CVD	EKG ECHO Lipid profile FBG	6, 12 months, Annually/Depending on symptoms
Liver	GVHD Hep B/C Iron Overload	LFTs Hep B/C viral load Ferritin (if multiple tranfusions), Imaging (if needed)	6, 12 months, Annually/ Depending on symptoms
GU	CKD UTI Bladder Dysfunction	BUN Urine Protein Serum Cr	6, 12 months, Annually/Depending on symptoms

Monitoring Post-Transplant

Tissue Organs	Complications	Procedure	Timing
Muscle and connective tissue	Myopathy Fasciitis/Scleroderma Polymyositis	Physical Activity ROM	6, 12 months, Annually
Mucocutaneous	Cutaneous Sclerosis Genital GVHD	Skin Exams Pelvic Exams	6, 12 months, Annually
Skeletal	Osteopenia/Osteoporosis Avascular necrosis	DEXA (women/all allo-HCT patients) MRI	12 months, Annually /Depending on symptoms
CNS	Neuropsychological /Cognitive defects Peripheral Neuropathy Late Infections	Neuropsych testing *MRI	12 months, Annually /Depending on symptoms

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NMDP guidelines

Monitoring Post-Transplant

Tissue Organs	Complications	Procedure	Timing
Endocrinology	Hypothyroidism Hypogonadism Hypoadrenalism Growth Retardation	TSH FSH/LH /Testosterone Growth Velocity	12 months, Annually /Depending on symptoms
Psychosocial and Sexual health	Anxiety Depression Fatigue Sexual Dysfunction	Mental dysfunction *Query Sexual health	6 /12 months, Annually/ Depending on Symptoms
Fertility	Infertility	FSH/LH Reproductive Health referral	12 months, Annually /Depending on symptoms
General	Secondary malignancies	Screening guidelines	6/12 months, Annually /Depending on symptoms

NMDP guidelines

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Thank you!