Introduction to Graft-versus-Host Disease (GVHD)

Celebrating a Second Chance at Life Survivorship Symposium

April 27 – May 3, 2024

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Graft-versus-Host Disease: The Basics

BMTinfonet.org - Symposium 2024
April 27 2024

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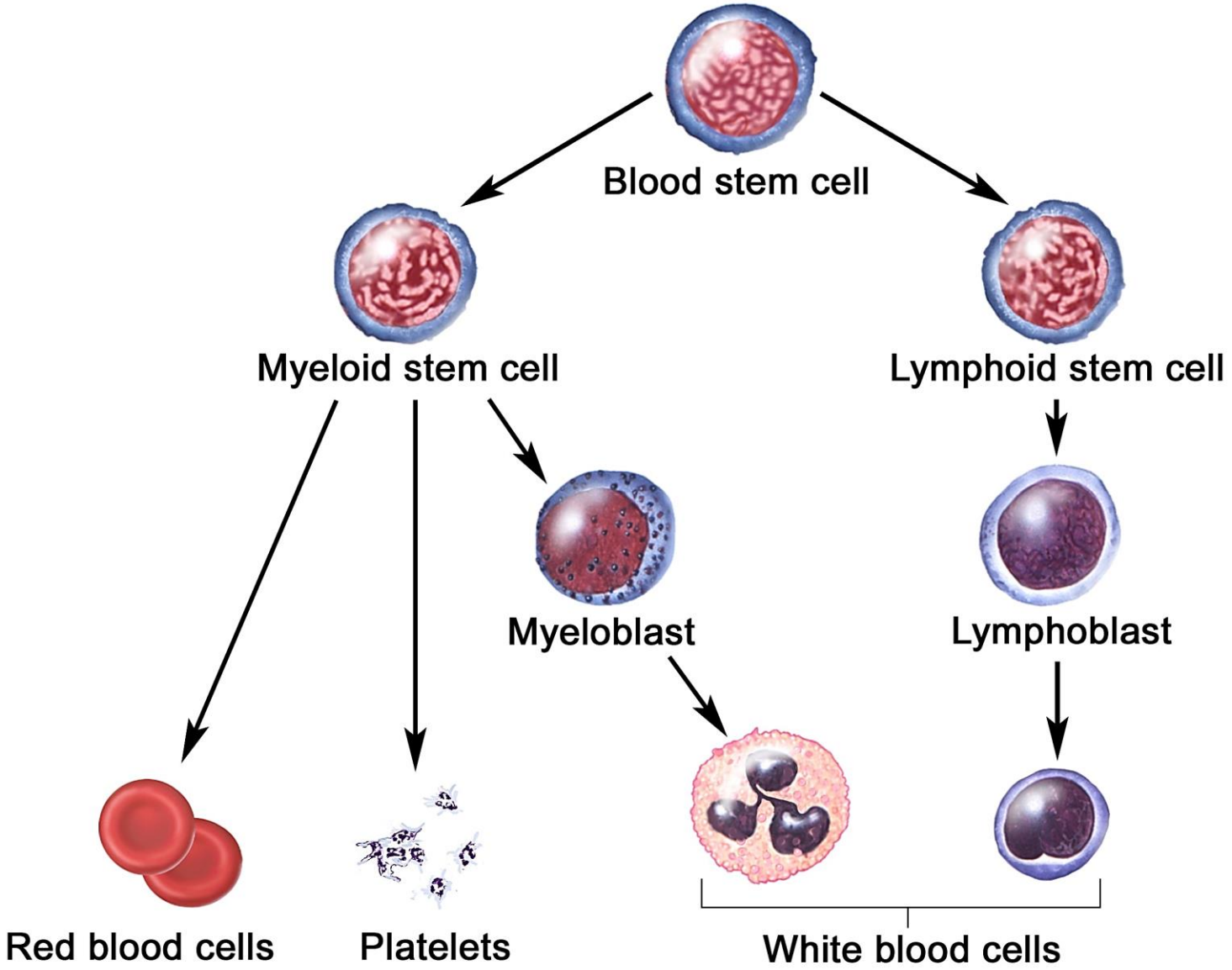
Introduction to Graft-versus-Host Disease (GVHD)

- Allotransplant: A quick introduction.
- Mechanisms leading to GVHD
- Incidence and risk factors GVHD
- Clinical presentation of GVHD
- GVHD prophylaxis
- GVHD treatment



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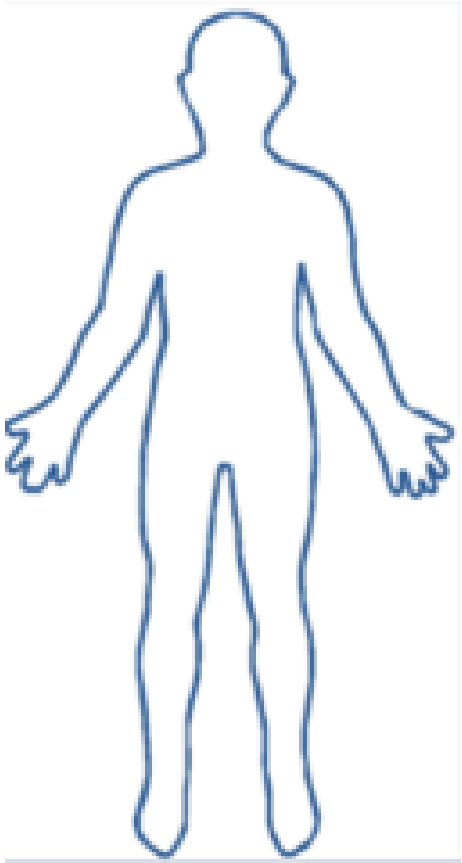
Transplant from Donor

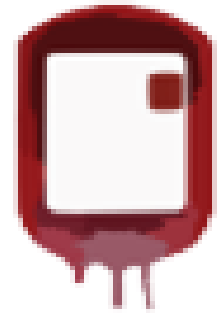


Recipient

"Host"

Blood forming cells: STEM CELLS

- Replace Host's stem cells



Immune Cells:

- They can attack the recipient
  - "Graft versus host disease"
- They can destroy cancer cells
  - "Graft Versus Tumor"

Graft-versus-Host Disease (GVHD)

- Biological consequence of the transfer of a donor's immune cells into the recipient
- Immunosuppressive medications are necessary to prevent GVHD
- GVHD can be eliminated by removing immune cells (T-cells) from the donor collection

GVHD How Does It Happen? Elements of Over-Reactivity

Chemo and radiation :**Tissue damage**

Damage to **intestinal** environment

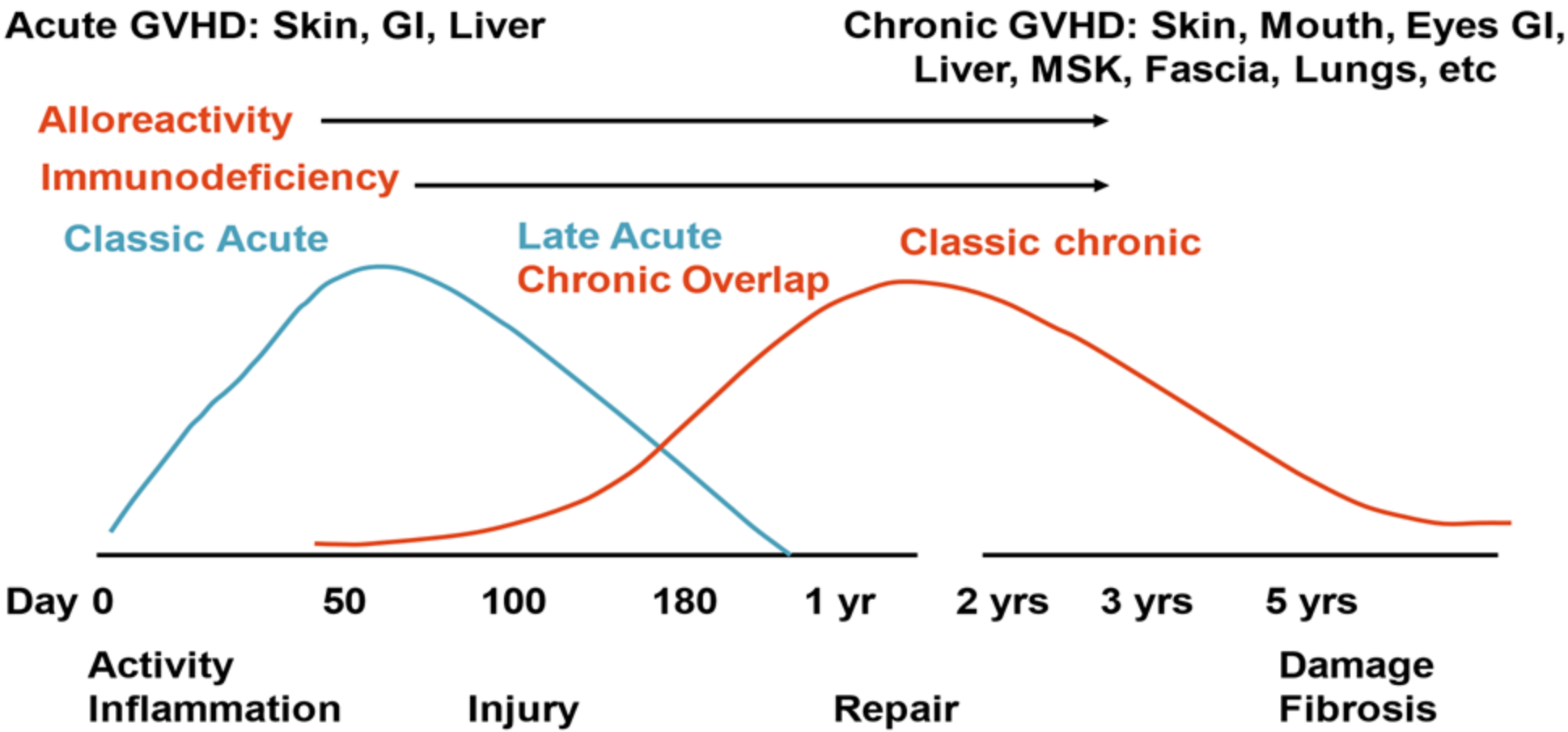
Cytokines and **inflammatory mediators**

Donor immune cells **discover host targets**

Cells **cross talk** amplifies and direct **fight to many directions**

Issues in ***control*** and ***education*** the immune cells

GVHD: Acute and Chronic



Cutler BMTinfo 2020

Acute Graft-versus-Host Disease (GVHD)

- Leading cause of mortality
- Grade II-IV occurs in ~70% pts
- Grade III-IV occurs in 10-15%
- ***~2-6 weeks after transplant***
- 30-40% refractory to 1st line of treatment

Acute GVHD - Risk Factors

Factor	↑ Risk of acute GVHD
Donor-recipient factors	
HLA disparity (HLA class I, II)	***HLA mismatched > matched donor***
Minor HLA disparity (mHA)	Unrelated donor > related donor
Sex matching	Mismatch > match
Donor parity	***Multiparity > nulliparity***
Donor age	Older donor > younger donor
ABO type	ABO mismatch > ABO match
Donor CMV serostatus	CMV positive > CMV negative
Cytokine gene polymorphisms	Numerous associated with acute GVHD
Stem cell graft factors	
Stem cell source	PBSC > BM > UCB
Graft composition	Higher CD34+ count > lower CD34+ cell count Higher T-cell dose > lower T cell dose
Transplantation factors	
Conditioning intensity	Myeloablative > reduced-intensity regimens

Acute GVHD: Clinical Features and Grading - MAGIC

GVHD Target Organ Staging

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (stool output/day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	<500 mL/day or <3 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	500-999 mL/day or 3-4 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL		1000-1500 mL/day or 5-7 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		>1500 mL/day or >7 episodes/day
4	Generalized erythroderma (>50% BSA) *plus* bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based on most severe target organ involvement):
Grade 0: No stage 1-4 of any organ.
Grade I: Stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade III: Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI.
Grade IV: Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

Harris et al, BBMT 2016

Chronic Graft-versus-Host Disease (GVHD)

- Most serious and common long-term complication of transplant
- Occurs in **30% - 55% of patients**
- ~4-6 months after transplant
- 50% of patients have 3 or more organs involved
- On average, therapy is required for 2-3 years

Organ/site	Diagnostic	Distinctive *(insufficient for diagnosis)*	Features seen in acute & chronic GVHD
Skin	· Poikiloderma · Lichen planus-like · Sclerosis · Morphea-like · Lichen sclerosis-like	· Depigmentation · Papulosquamous	· Erythema · Maculopapular · pruritus
Nails		· Dystrophy · Onycholysis	
Scalp/body hair		· Alopecia (scarring or nonscarring) · Scaling	
Eyes		· New dry, gritty, or painful eyes (sicca) · Keratoconjunctivitis · Punctate keratopathy	
Genitalia	· Lichen planus-like · lichen sclerosis-like · Vaginal or urethral scarring/stenosis · Labial agglutination · Phimosis	· Erosion · Fissures · Ulcers	
Mouth	· Lichen planus-like	· Xerostomia · Mucoceles · Mucosal Atrophy · Pseudomembranes · Ulcers	· Gingivitis · Mucositis · Erythema · pain

Organ/site	Diagnostic	Distinctive *(insufficient for diagnosis)*	Features seen in acute & chronic GVHD
GI tract	· Esophageal web · Esophageal strictures		· Diarrhea · anorexia · Nausea vomiting · Malabsorption · Wasting syndrome/FTT
Liver			· Mixed hepatitis, · Increased TBili, ALP, ALT
Muscles, fascia, joints	· Fasciitis · Joint stiffness or contractures due to sclerosis	· Myositis · Polymyositis	
Lung	· Bronchiolitis obliterans (bx)	· Cryptogenic organizing pneumonia (COP or BOOP) · Restrictive lung disease	
Heme/ Immuno		· Thrombocytopenia · Eosinophilia · Hypo-hypergamma · Autoantibodies · Raynaud phenomenon	
Others		· Serositis/effusions · Nephrotic syndrome · Myasthenia gravis · Peripheral neuropathy · Whole body anasarca	

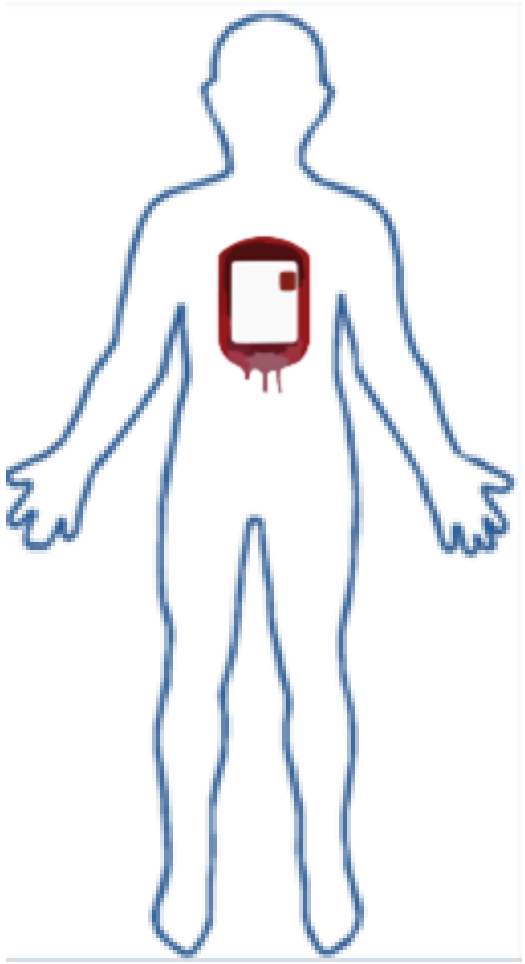
Chronic GVHD: 2014 NIH Consensus

Mild	• 1 or 2 organs or sites (except lung) with score 1
	  • Mild oral symptoms, no decrease in oral intake
	  • Mild dry eyes, lubricant eyedrops ≤ 3x/day

Moderate	• 3 or more organs with score 1
	• At least 1 organ or site with score 2
	  • 19-50% body surface area involved or superficial sclerosis
	  • Moderate dry eyes, eyedrops > 3x/day or punctal plugs
	• Lung score 1 (FEV1 60-79% or dyspnea with stairs)

Severe	• At least 1 organ or site with score 3
	  • > 50% body surface area involved
	  • Deep sclerosis, impaired mobility or ulceration
	  • Severe oral symptoms with major limitation in oral intake
	  • Severe dry eyes affecting ADL
	• Lung score 2 (FEV1 40-59% or dyspnea walking on flat ground)

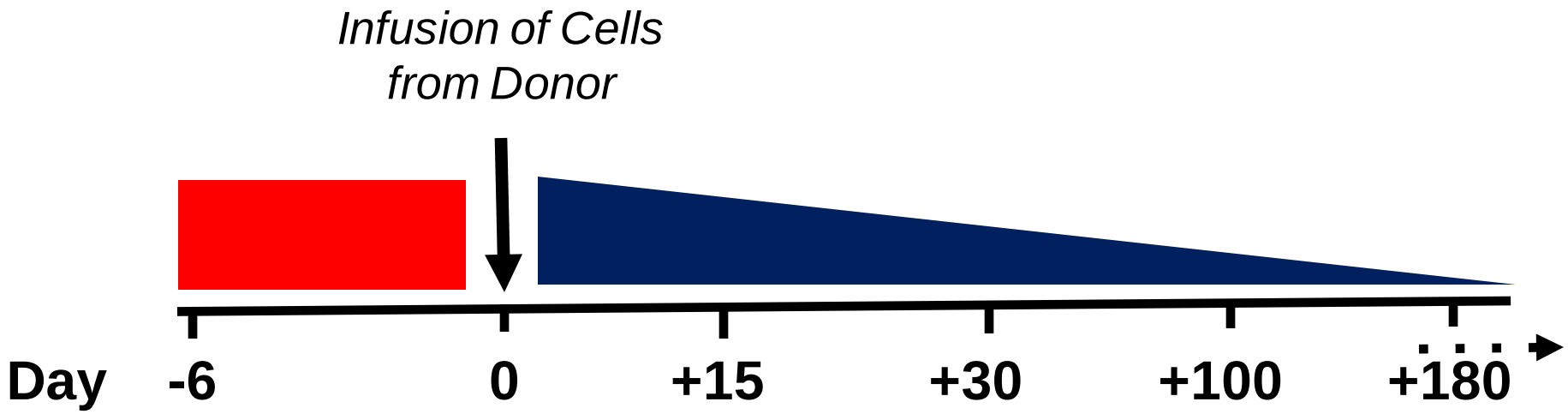
Transplant from Donor: How to Define Success



Tolerance

- Cure the blood cancer
- NO Graft-versus-Host Disease

Transplant from Donor: General Schema



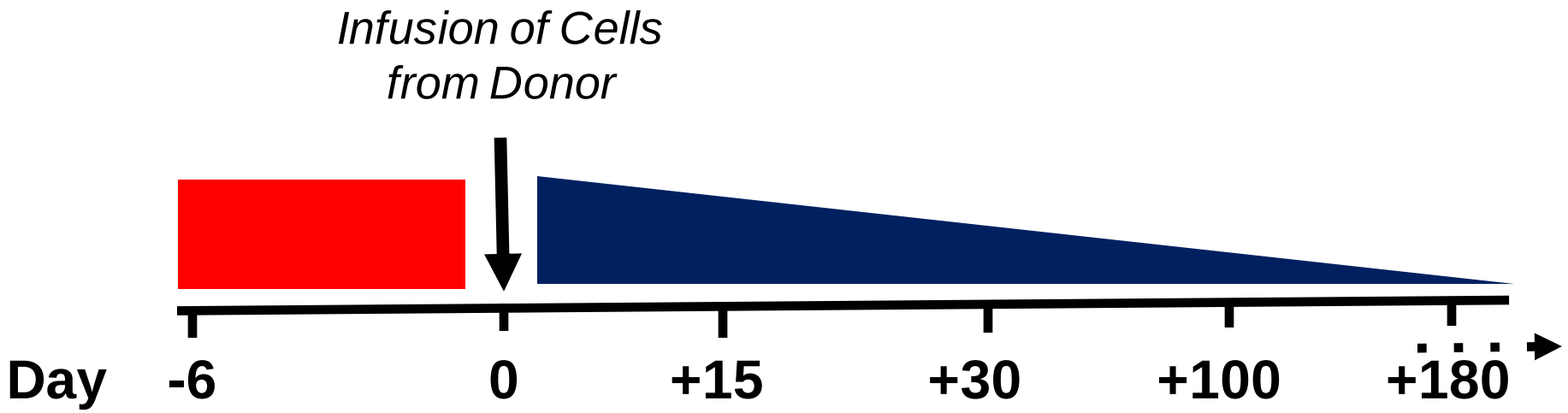
CONDITIONING

- ✓ Chemo +/- Radiation
- ✓ More or less intense
- ✓ Prevent Rejection
- ✓ Destroy cancer cells

POST TRANSPLANT IMMUNOSUPPRESSION

- ✓ Drugs given in vein or by pills
- ✓ Prevent GVHD

Transplant from Donor: General Schema



CONDITIONING

- ✓ Chemo +/- Radiation
- ✓ Prevent Rejection
- ✓ Destroy cancer cells

Cyclosporine + Methotrexate Tacrolimus + Methotrexate

Tacrolimus + MMF

Tacrolimus + Sirolimus + MMF

Tacrolimus + Methotrexate + Abatacept

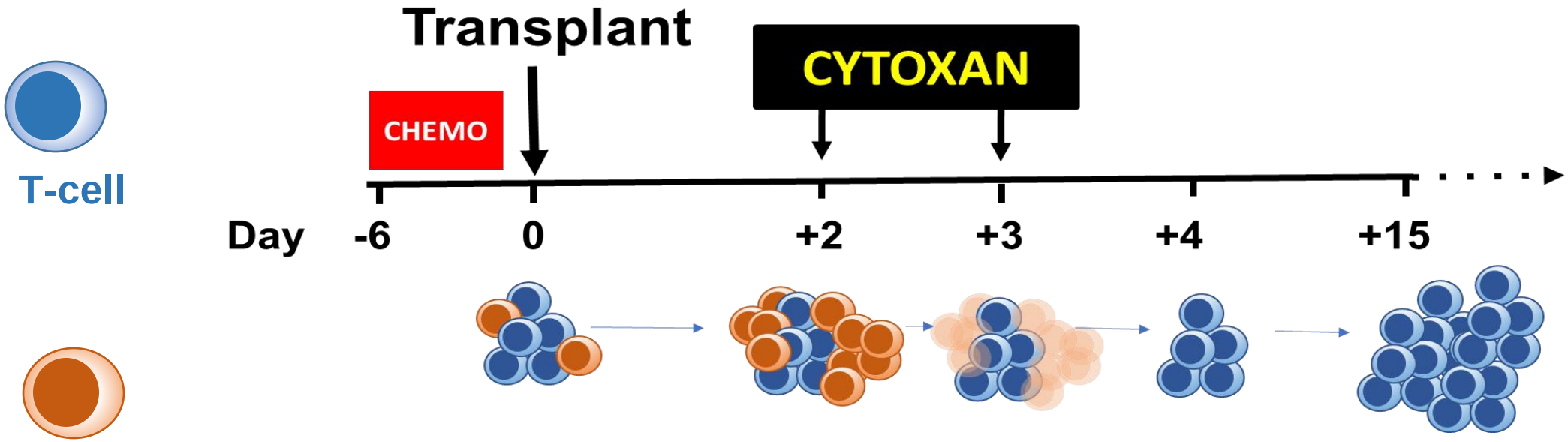
Other Ways to Reduce GVHD: Look at the Donation

- In the donor collection bag there is a mix of many kinds of cells:
  - Stem cells and LOTS and LOTS of immune cells.
- Some cells can induce GVHD (Naïve T cell)
  - ***ALLOREACTIVE – BAD guys***
- Some cells can prevent or reduce GVHD (Regulatory T cells)
  - ***TOLERANCE – GOOD guys***

Strategies to Avoid GVHD

- Post-transplant Cytoxan (PTCy)
- Graft manipulation

How Post-Transplant Cytoxan (PTCy) Works



Alloreactive T-cell
cause GVHD (the BAD ones)

Alloreactive T-cell
expand and are
destroyed by Cytoxan

All other
T-cells
thrive

Post-Transplant Cytoxan (PTCy): Study and Clinical Data

- PTCy (+TAC/MMF) already used worldwide for transplant from children or parents (haploidentical transplants)
- BMT CTN 1203 clinical trial showed promising results in transplants from siblings and unrelated donors.
- **Phase III BMT CTN 1703** study evaluated outcomes after **reduced-intensity conditioning** transplant in patients randomized to receive PTCy + TAC + MMF vs standard TAC+ MTX

PTCy = post-transplant cyclophosphamide
TAC = tacrolimus
MMF = mycophenolate mofetil
MTX = methotrexate

Holtan et al ASH 2022

BMT CTN 1703: Results

	PTCy + TAC + MMF *(n = 214)*	TAC + MTX *(n = 217)*
Patients living without disease and without GVHD 1 year post transplant	**53%**	**35%**

PTCy= post-transplant cyclophosphamide
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Holtan et al ASH 2022

BMT CTN 1703: Results

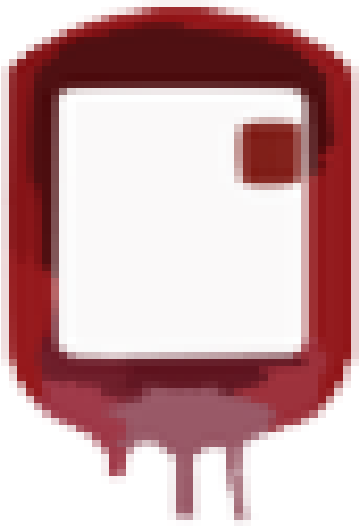
	PTCy + TAC + MMF *(n = 214)*	TAC + MTX *(n = 217)*
Patients with **acute GVHD** 100 days post transplant	**6%**	**15%**
Patients with **chronic GVHD** 1 year post transplant	**12%**	**25%**
Patients with **Cancer Relapse** 1 year post transplant	**21%**	**20%**
Transplant mortality 1 year post transplant	**12%**	**17%**

Holtan et al ASH 2022

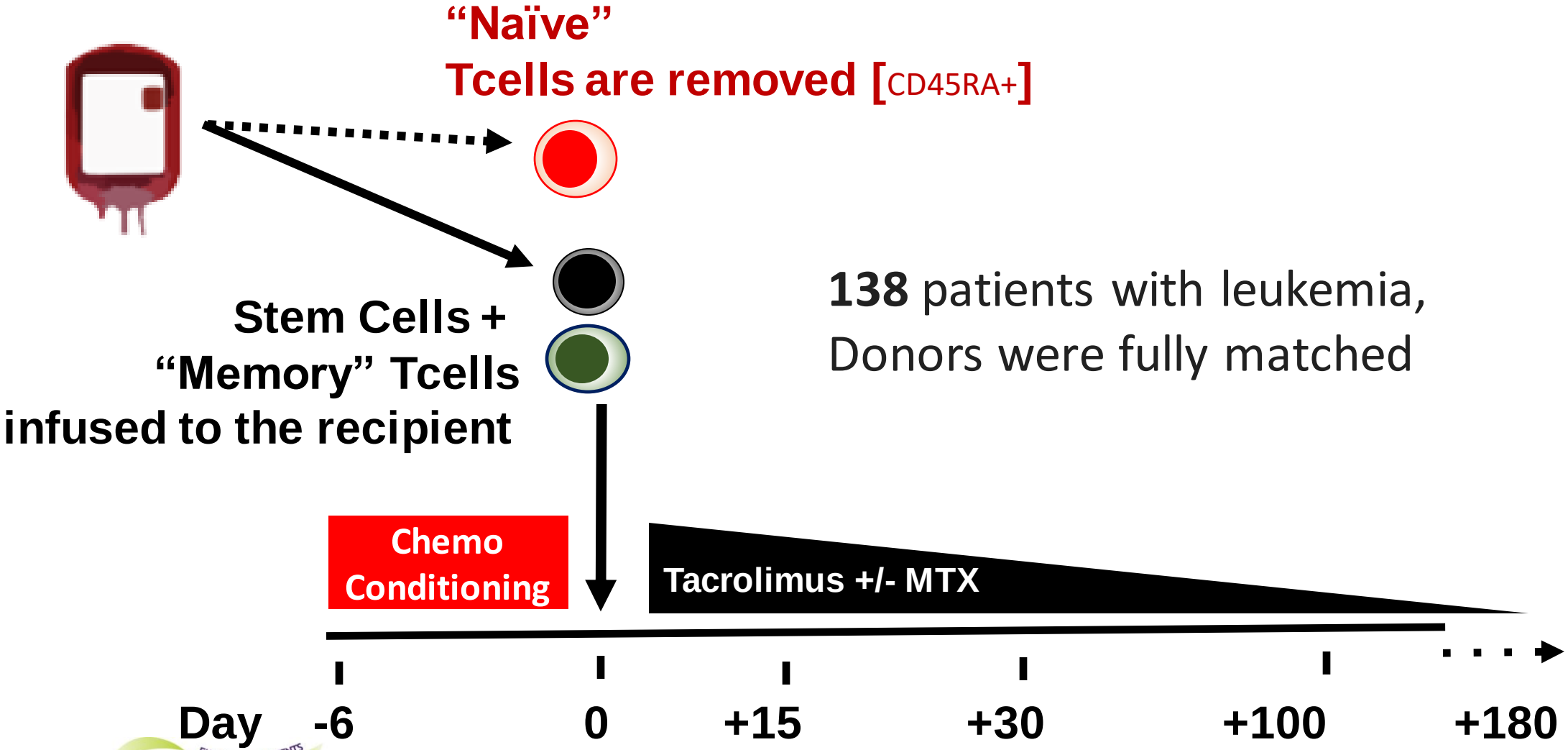
Other Ways to Reduce GVHD

Donor collection :

- Let’s remove the bad guys
- Let’s help the good guys



“Let’s Remove the BAD Guys” Approach



Bleakley et al JCO 2022

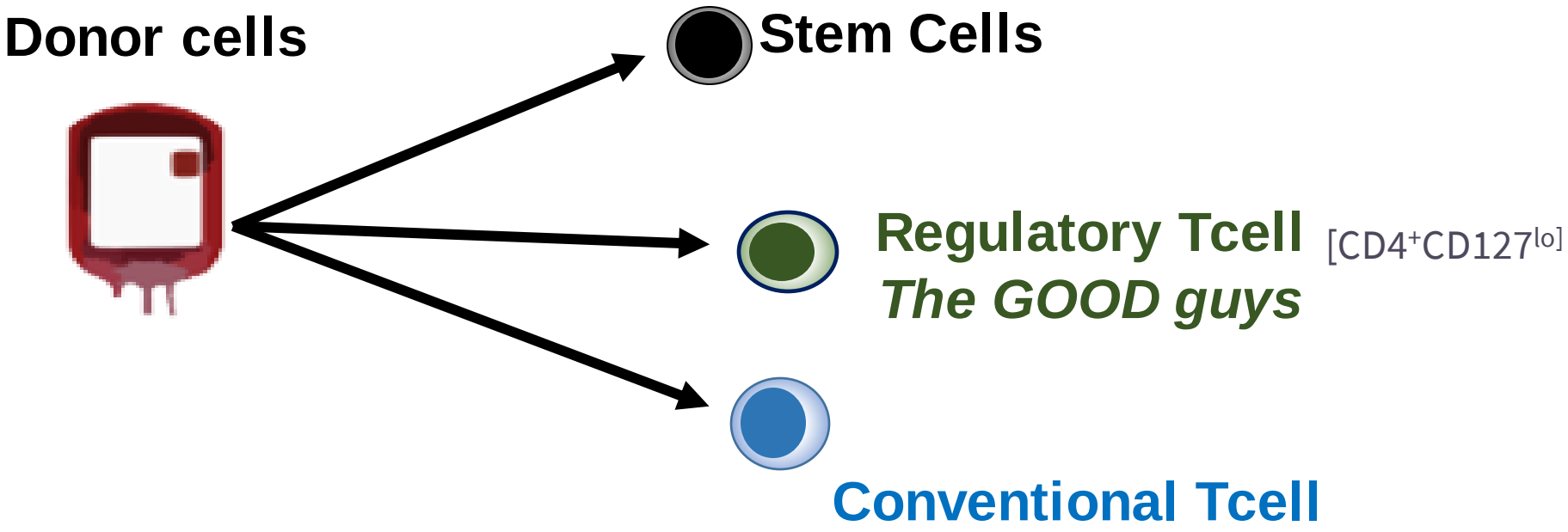
“Let’s Remove the BAD Guys” Approach

	“Naïve” T-cell depleted *(n = 138)*
Patients with **acute GVHD grade ≥3** 180 days post transplant	**4%** **None severe**
Patients with **chronic GVHD** 1 year post transplant	**7%** **None severe**
Patients living without disease and without GVHD 3 years post transplant	**68%**
Overall Survival 3 years post transplant	**77%**

Bleakley et al JCO 2022

“Let’s Help the GOOD Guys” Approach

ORCA-T



Oliai et al, ASH 2022

ORCA-T: Clinical Trials

- **127 patients**, with high-risk blood cancers
- Donors were fully matched related (n=66) or unrelated (n=61).
- Transplant was with high dose chemo or radiation
- Post transplant single-agent tacrolimus
- Outcomes were compared with 375 matched patients from the CIBMTR registry

NCT04013685
NCT01660607

Oliai et al, ASH 2022

ORCA-T: Results

	ORCA-T *(n = 127)*	CIBMTR Control *(n = 375)*
Patients with **acute GVHD grade ≥3** 180 days post transplant	**5%**	**16%**
Patients with **chronic GVHD** 1 year post transplant	**6%**	**38%**
Relapse free survival 1 year post transplant	**81%**	**62%**
Non Relapse mortality 1 year post transplant	**5%**	**10%**
Overall Survival 1 year post transplant	**91%**	**68%**

Oliai et al, ASH 2022

ORCA-T: Results

	ORCA-T *(n = 127)*	CIBMTR Control *(n = 375)*
Patients living without disease and without GVHD 1 year post transplant	**76%**	**34%**

A multi-center randomized controlled phase 3 trial comparing Orca-T to standard of care is currently enrolling across the US (NCT05316701).

Oliai et al ASH 2022

GVHD Treatment: Principles

- Steroids: mainstay of systemic treatment
- Acute: **40-60%** respond < 5 days
- Chronic: need longer course (ie. weeks to months)
- **When steroids don't work:** several options are available

GVHD: Challenges

- No one treatment fits all patients
- Some therapies are ineffective
- Treatment has side effects, immunosuppressive, might be needed lifelong
- Impact on quality of life, return to family life, relationships, work

New Drugs Approved for GVHD Treatment

	Type of GVHD	FDA approved
Ibrutinib (Imbruvica®)	Chronic	2/8/2017
Ruxolitinib (Jakafi®)	Acute	5/24/2019
	Chronic	9/22/2021
Belomosudil (Rezurock®)	Chronic	7/16/2021

Ibrutinib (Imbruvica®)

- Original study included 42 patients with bad GVHD, resistant to steroids
  - In 31% of patients, GVHD went away completely
  - 38% of patients had partial resolution of GVHD
  - In 55% of patients, the response lasted at least 11 months
  - 64% of patients could reduce the usage of steroids like prednisone
- **It works on sclerotic GVHD:**
  - 61% of patients with sclerosis showed improvement and in 39%, tightening of the skin went away

Waller EK, BBMT 2019
PCYC-1129-CA

Ibrutinib (Imbruvica®) Adverse Effects

- In > 20% of Patients
  - Fatigue
  - Bruising
  - Low platelets
  - Muscle spasm
  - Nausea
  - Pneumonia
  - Mouth sores

In ~5% of patients

- Irregular heartbeat

Ruxolitinib (Jakafi®)

- **Pill:** twice a day
- Already used for other blood diseases (myelofibrosis and Polycythemia Vera)
- **How does it work?**
  - *Modulates immune system* to switch off GVHD
  - Regulates the development, proliferation, and activation of several immune cell types.

Ruxolitinib (Jakafi®)

REACH2 Trial : Acute GVHD

- Randomly assigned 309 patients with severe steroid-refractory acute GVHD to receive ruxolitinib 10 mg twice daily (n = 154) or best available therapy (n = 155)
- Improvement was seen in **62%** of patients compared to 39%.
- GVHD went completely away in **34%** of patients on ruxolitinib vs 19% in the control group
- The good response was maintained after 2 months of treatment for more patients in the ruxolitinib group than in the control group (40% vs. 22%)

Zeiser R, NEJM 2020

Ruxolitinib (Jakafi®)

REACH3 Trial : chronic GVHD

- Randomly assigned 329 patients with moderate or severe steroid-refractory or dependent chronic GVHD to receive ruxolitinib 10 mg twice daily (n = 165) or best available therapy (BAT; n = 164)
- The improvement was seen in **50%** of patients compared to 26%.
- The responses lasted up to 1 year and 7 months
- **Patients reported improved quality of life and symptoms**

Zeiser R, NEJM 2021
Lee S, et al Blood. 2021

Ruxolitinib (Jakafi®) Adverse Effects

- >35%
  - Anemia
  - Low platelets
- >20%
  - Infection, fungal, viral
  - Liver tests go up

Belumosudil (Rezurock®)

- **Pill:** once or twice a day with food
- **Totally new drug designed to fight fibrosis (ROCK inhibitor)**
- **How does it work?**
  - Modulates immune system to switch off GVHD, does not depress the immune system
  - **Anti-fibrosis**

Belumosudil (Rezurock®)

- **77%** of patients treated improved
  - responses noted in all affected organs
- In 50% of patients, the response lasted at least 14 months
- Very well tolerated
- **Signals of response in patients who experienced treatment failure with ruxolitinib and ibrutinib.**

Cutler et al, Blood 2021
Study: ROCKstar

Belumosudil (Rezurock®) Adverse Effects

- ≥20%
  - Fatigue
  - Edema
  - Muscular pain
  - Liver tests go up
  - Headache
  - GI upset

Summary

- GVHD is a major complication of transplant
- We are getting better!
- Substantial strides have been made to prevent GVHD
- Promising additional therapies on the horizon
- Treatment for GVHD rapidly improving

Thank you !!!

BMT*infoNet*

Questions?

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