Latest Treatment and Advances for Chronic Graft-versus-Host Disease

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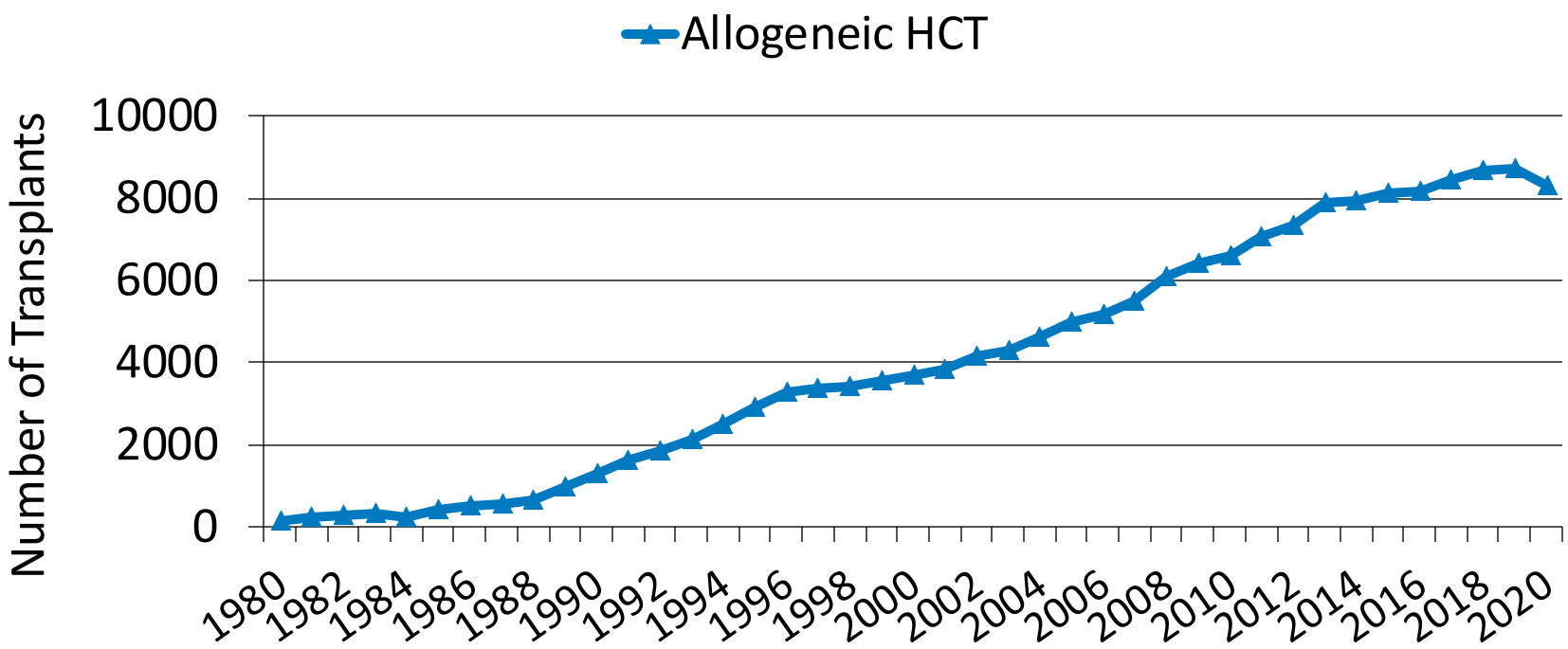
Agenda

- Introduction to the Graft-versus-Host Disease
- When Do I Need Treatment?
- What are We Trying to Achieve?
- Latest Treatments and Advances

Hematopoietic Stem Cell Transplantation

- Allogeneic hematopoietic stem cell transplantation (HCT) relies on an immunotherapy effect to cure advanced hematologic disorders or cancers
- A new donor bone marrow is established, producing blood and immune cells



Transplant is a marathon...

- Age/Genetics
- Comorbidity
- Psychosocial
- Lifestyle factors

Pre-HCT

- Chemotherapy, biologic, and radiation

HCT

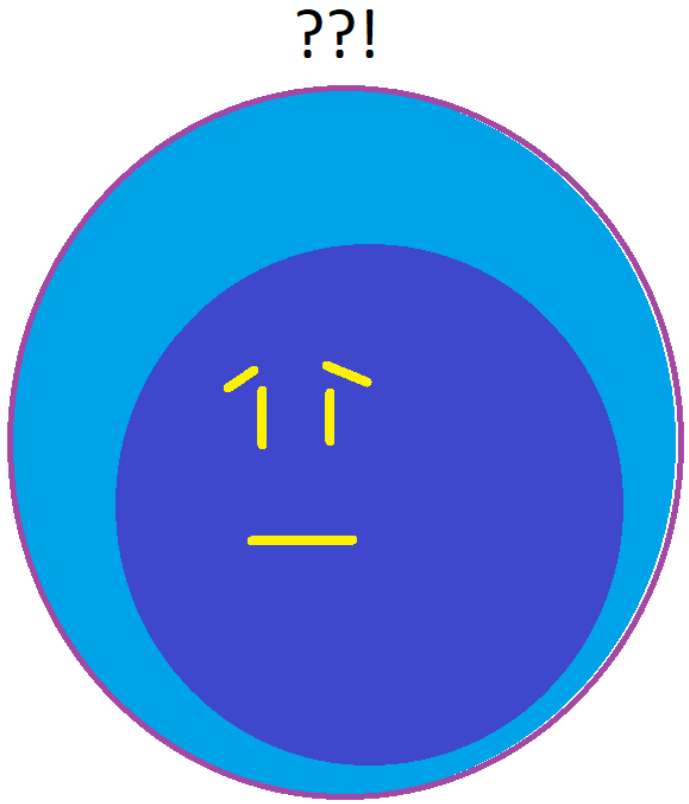
- HLA-match
- Conditioning chemotherapy
- Immune Suppression

Post-HCT

- Graft-versus-Host Disease (GVHD)
- Medications
- Health maintenance

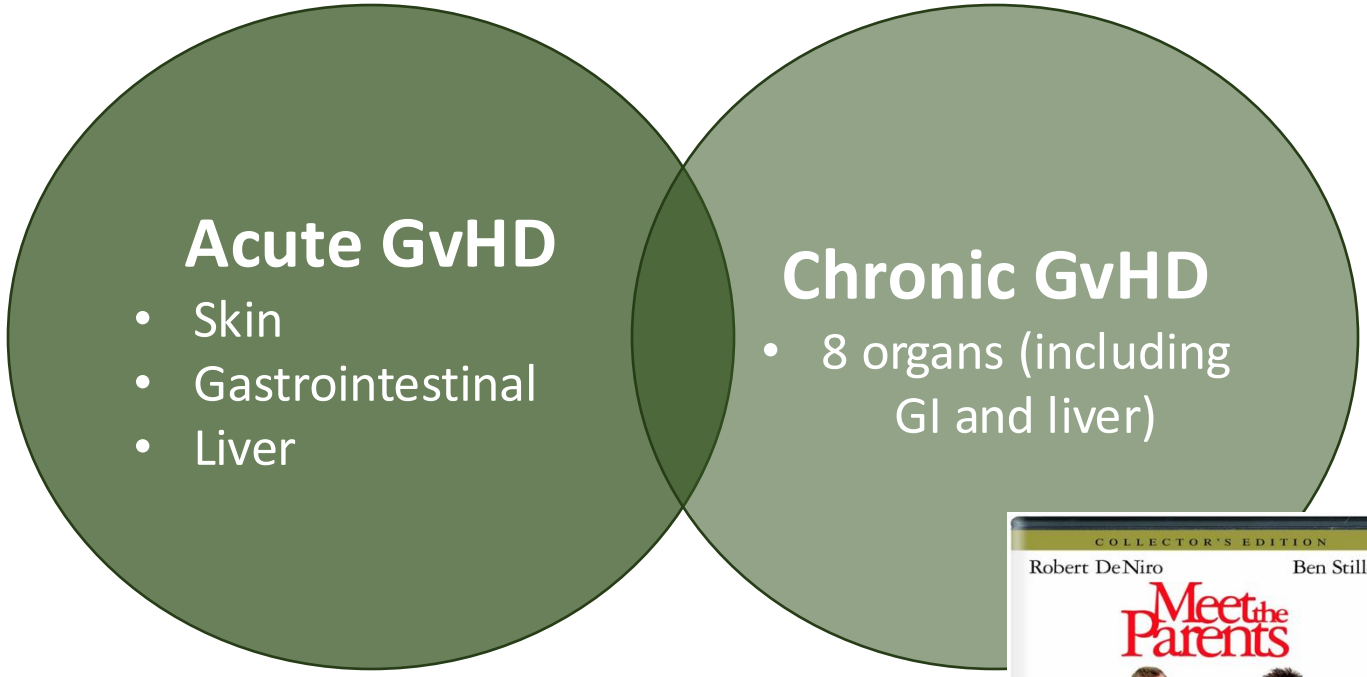
Graft-versus-Host Disease

- Donor stem cell transplant (HCT) relies on the Graft-versus-Cancer effect
- Graft versus Host phenomenon may result in “friendly fire”
- Leads to tissue damage due to donor immune system cells



Confused Lymphocyte

Graft-versus-Host Disease



Definitions and Subtypes

- Acute versus Chronic GVHD is classically defined in relation to Day + 100
- However, clinical findings differentiate between the acute or chronic GVHD diagnosis

Chronic GVHD (cGVHD)

- Most common long-term complication of HCT
- Affects 30-50% of HCT recipients
- Usually presents within 3 years after transplant
  - Frequency and manifestations are changing!
- Is a major cause of **problems** after HCT

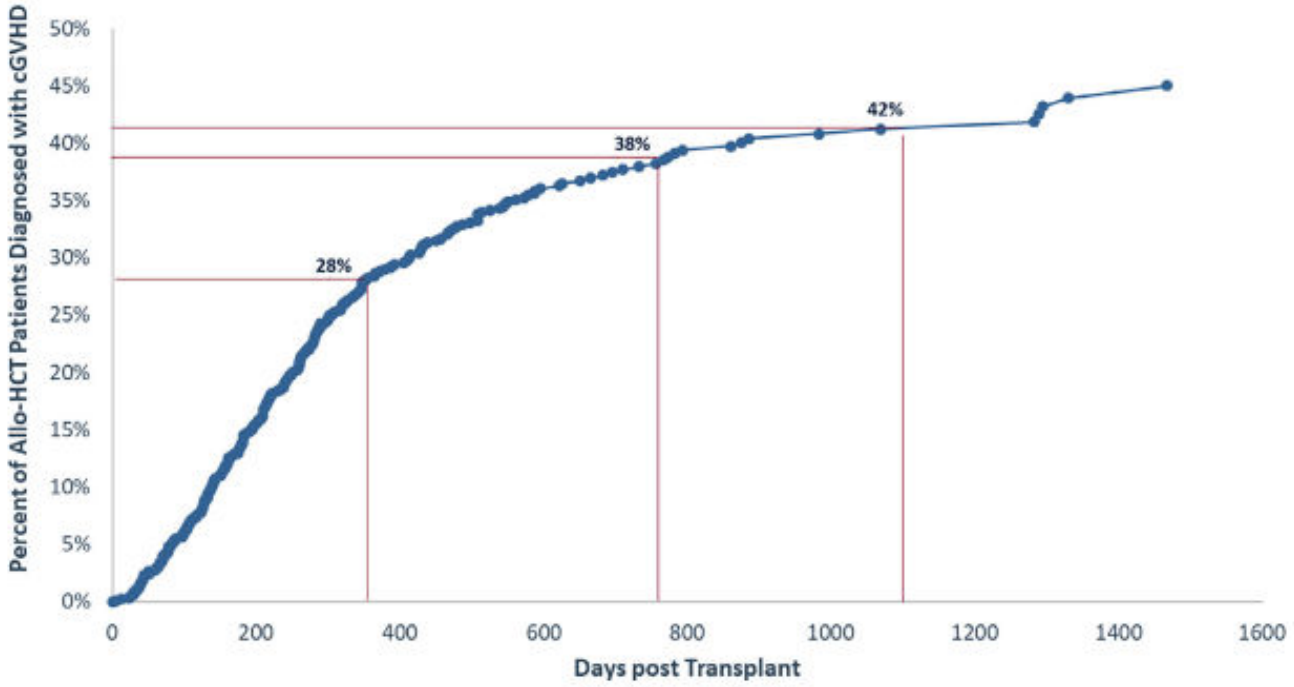


Figure 1. cGVHD cumulative incidence curve among allogeneic HCT recipients.

Bachier, et al. TCT 2020. (US Claims Analysis)

The Approach to Chronic GVHD

- Do Nothing (**Observe**)
- Do Something (**Treat**)
  - Treatment a local area (**Topical**)
  - Treat the entire body (**Systemic**)

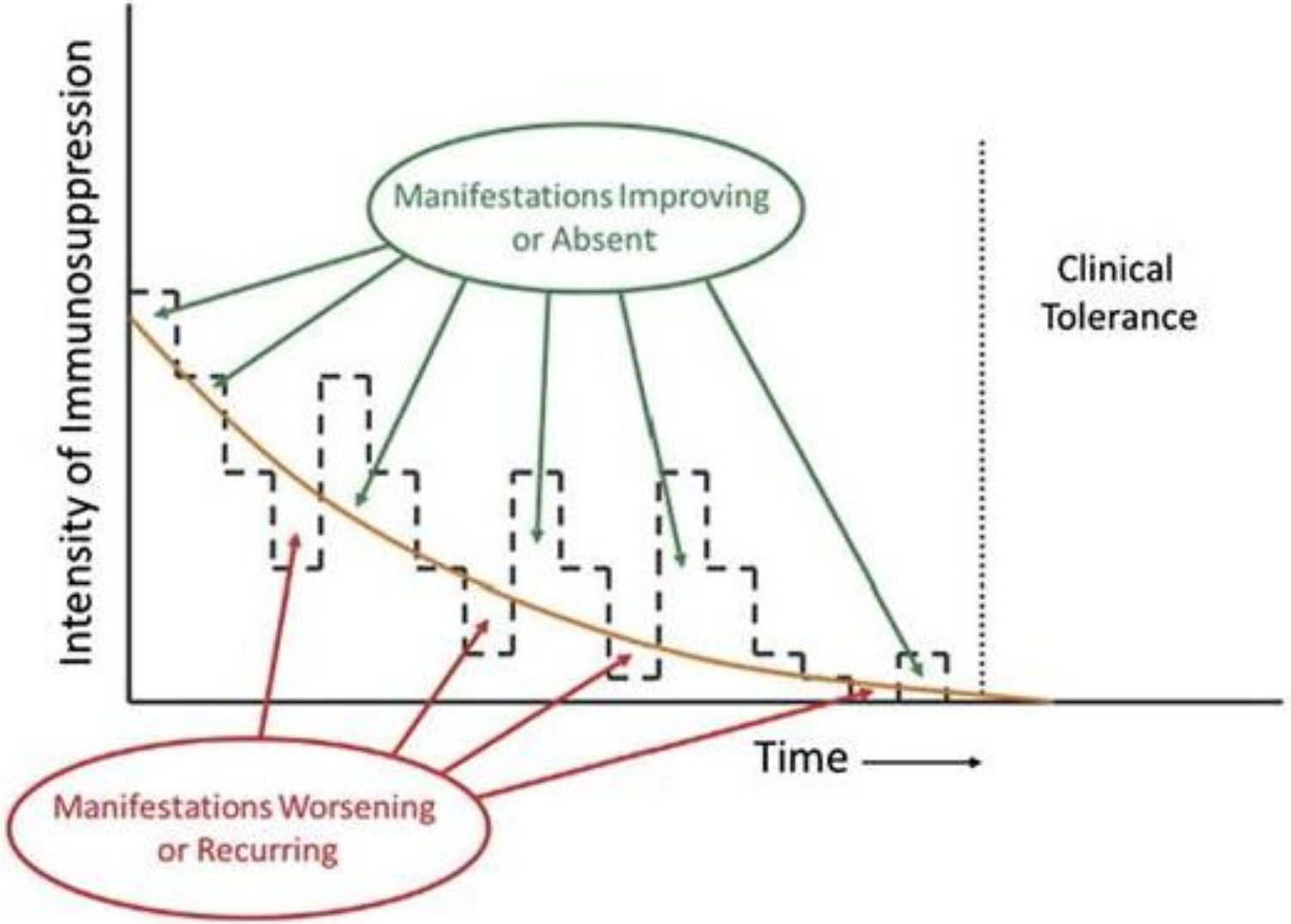
Too much treatment

Infection and drug related toxicity

Too little treatment:

Irreversible organ damage, quality of life impairment

The GVHD Balancing Act



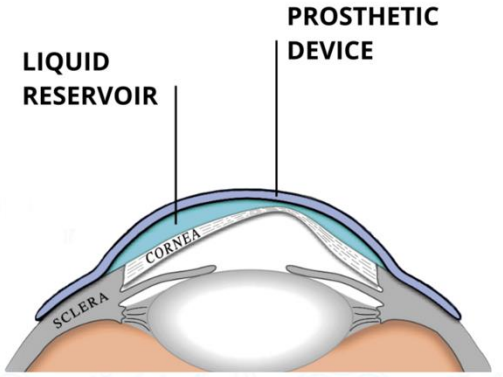
Flowers, Martin. Blood 2015.

Skin

- Control pain/neuropathy
- Prevent/reduce joint tightening
- Prevent/reduce ulceration and infection
- Prevent/reduce skin cancer development

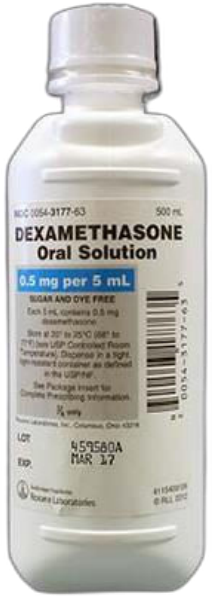
Eye

- Control symptoms (dry eye, pain)
- Prevent scarring
- Prevent vision loss



Oral

- Reduce pain and sensitivity
- Prevent/reduce mouth scarring
- Prevent/reduce jaw tightness
- Prevent oral cancer development



Gastrointestinal

- Control symptoms (nausea, weight loss, swallowing difficulty)

Liver

- Reduce chronic inflammation, preserve function

Lung

- Preserve lung function

Joint/Fascia

- Reduce pain or weakness
- Improve or stabilize range of motion

Genitourinary

- Control pain/symptoms
- Enhance sexual health and satisfaction

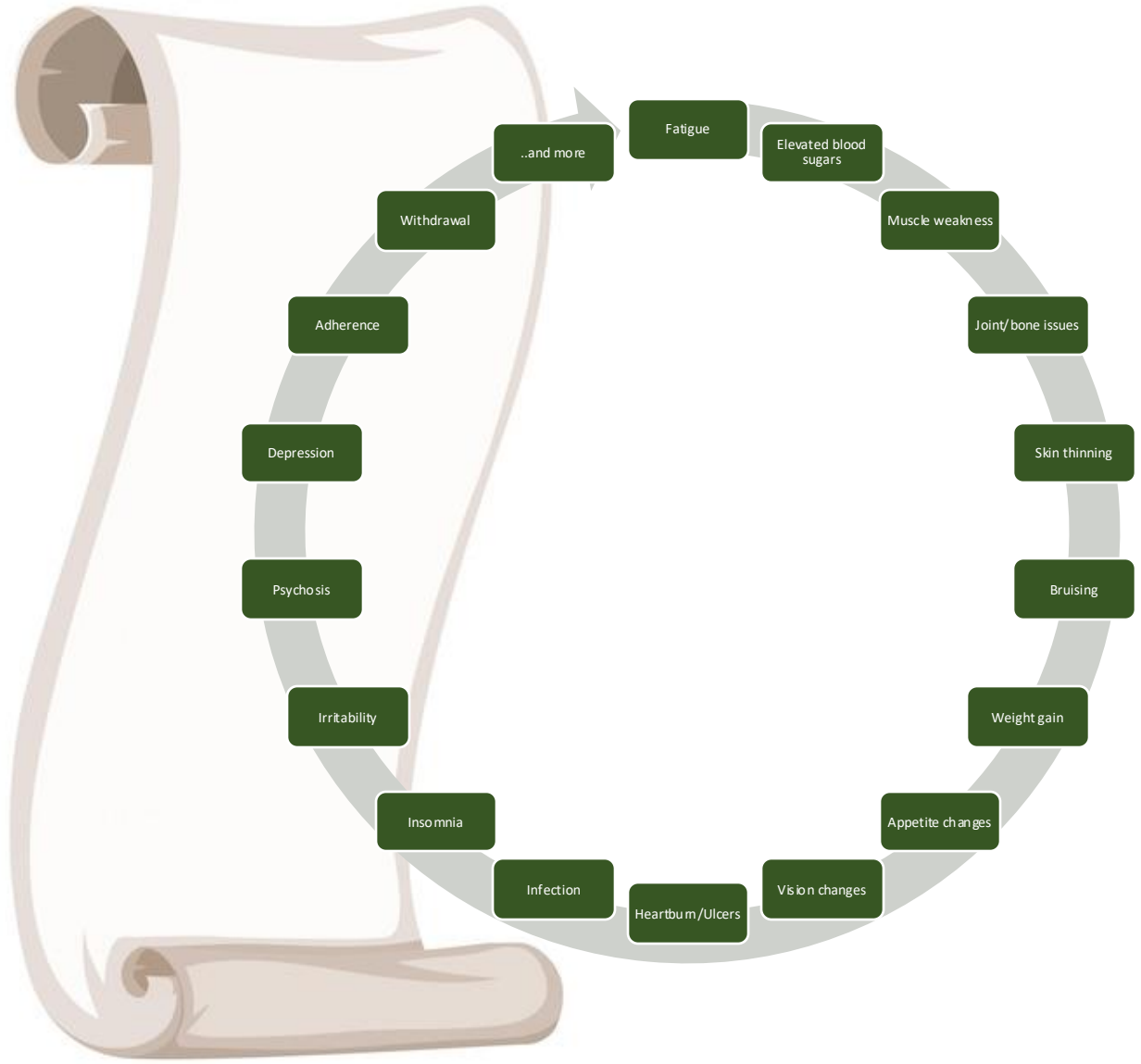
When Treatment is Needed

- Standard of Care: prednisone 1mg/kg/day
  - Sometimes combined with an additional immune suppressant
- Improvements seen in > 60% of patients
- Difficult to discontinue in cGVHD
- Side effects!

Day	Dose, mg/kg Body Weight
1	Current QD dose of corticosteroid (eg, 1 mg/kg per day)
7-14	Current dose of corticosteroid (eg, 1 mg/kg per day); Decrease alternate day dose by 50% (0.5 mg/kg per day)
28	Current dose of corticosteroid (1 mg/kg per day); Decrease alternate day dose by 50% (0.25 mg/kg per day)
42	Current dose of corticosteroid (1 mg/kg), QOD
56	Decrease current dose of corticosteroid by 10% every week until off

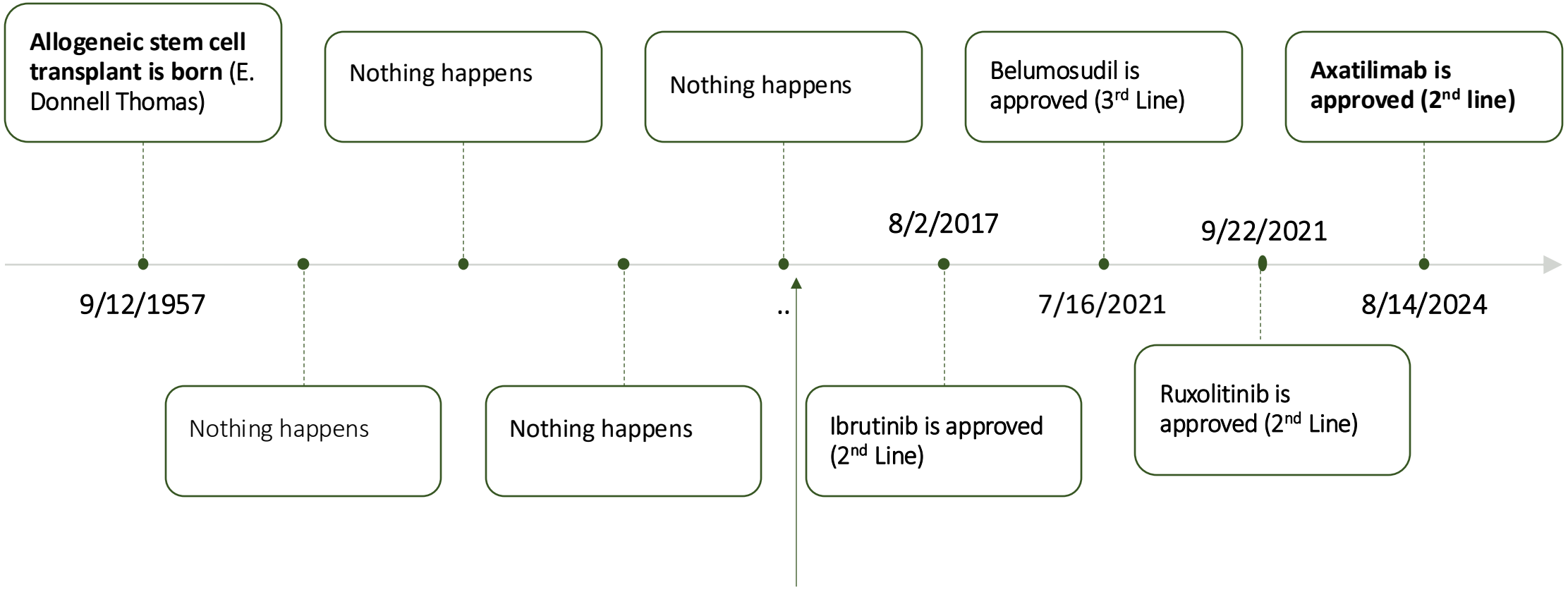
Flowers, Martin. Blood 2015.

The Dark Side of Corticosteroids

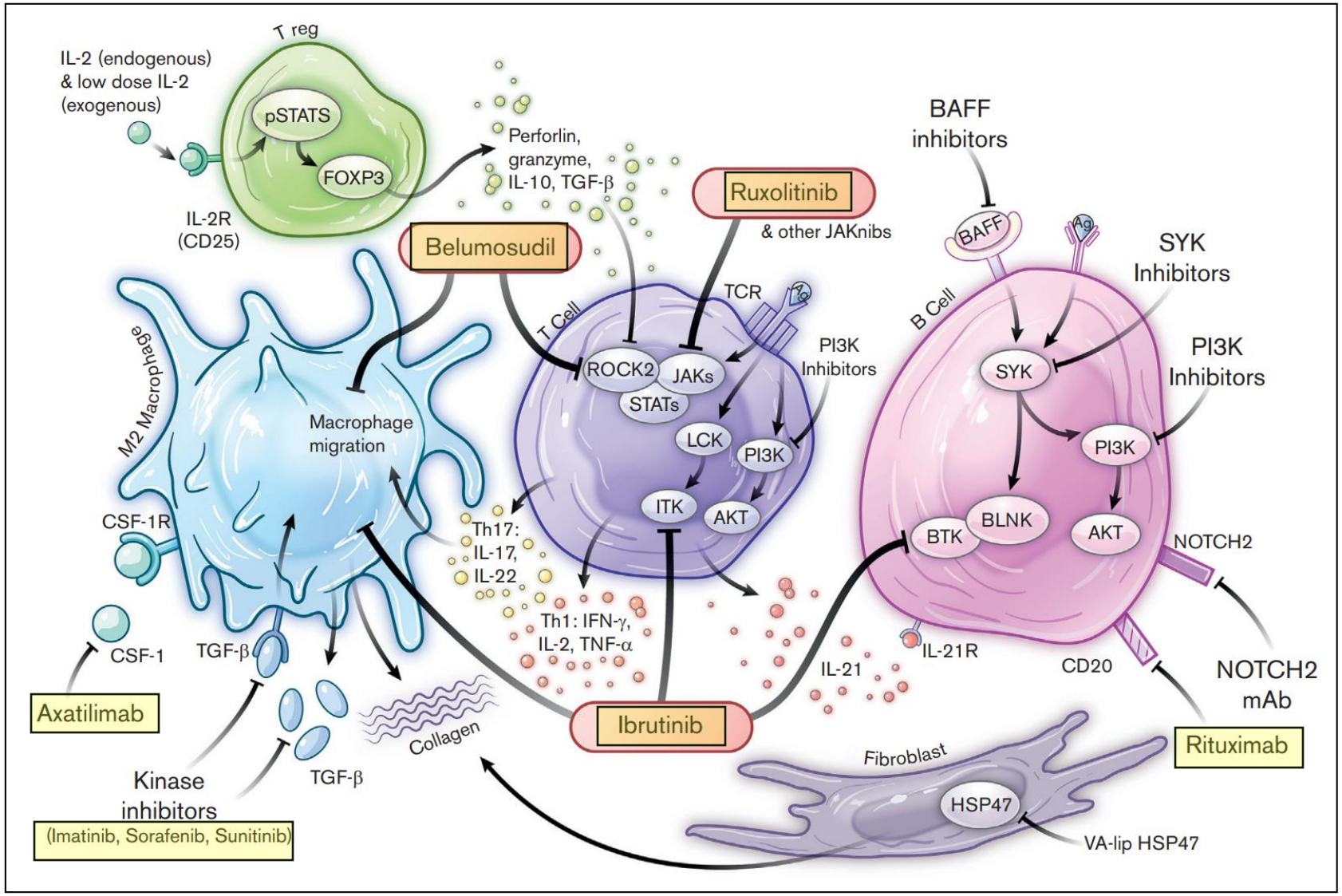


- Works by weakening the immune system ➡ Need to monitor for infections
- Symptoms may recur or worsen if corticosteroids are reduced

Progress in FDA Approvals for cGVHD



Targeted Approaches to cGVHD Treatment



Buxbaum, et al. Blood Adv 2023

Ibrutinib

- Initially FDA approved for Chronic Lymphocytic leukemia, but approved 8/2/17 for cGVHD after failure of 1 or more lines of therapy
- Works by suppressing immune response in B and T cells
- May be more useful in patients with red rash or mouth GVHD (redness)
- Notable Side effects: infection, diarrhea, fatigue, heart issues including arrhythmias

Miklos, et al. Blood 2017

Belumosudil

- FDA approved **7/16/2021** after failure or 2 or more lines of therapy
- Targets fibrotic (scar) related pathways and rebalances immune system
- Pre-treated patients >= 2 lines of prior therapy
- Fairly well tolerated

Ruxolitinib

- FDA approved **9/22/21** after failure of at least one prior line
- Targets inflammation pathways (JAK/STAT)
- Has the largest clinical trial study with comparison group
- Side effects: blood counts, weight gain, infection

Zeiser, et al. NEJM 2021.

Axatilimab

- FDA approved **8/14/24**
- Targets pro-inflammatory and scarring-related immune system monocytes/macrophages
- **Intravenously administered** every 2 weeks
- Notable Side effects: liver enzyme elevation, eye swelling

Kitko, Wang, et al. JCO 2023.

Extracorporeal Photopheresis

- Not FDA approved, but commonly used (and covered by insurance companies) for treatment of refractory GVHD
- Rebalances immune system, but exact mechanism is not clear
- **Intravenous "blood exchange" treatment**
- Time commitment
- Notable side effects: fatigue/lightheadedness, catheter/port access site problems, photosensitivity

Closing Thoughts

- Progress is being made in cGVHD
  - **Watch for**: new or worsening symptoms and signs of cGVHD, both physical and mental
  - **Watch for**: risk of infections
  - **Don’t Forget**: Health maintenance and routine cancer screenings
  - **New treatment trials**: focusing on steroid-free regimens, new combinations, and organ-specific treatments
  - **Also needed:** focus on behavioral health and survivorship, implement more digital health platforms

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Thank you