

Overview of GVHD Management:

A Clinician's Guide and Resource



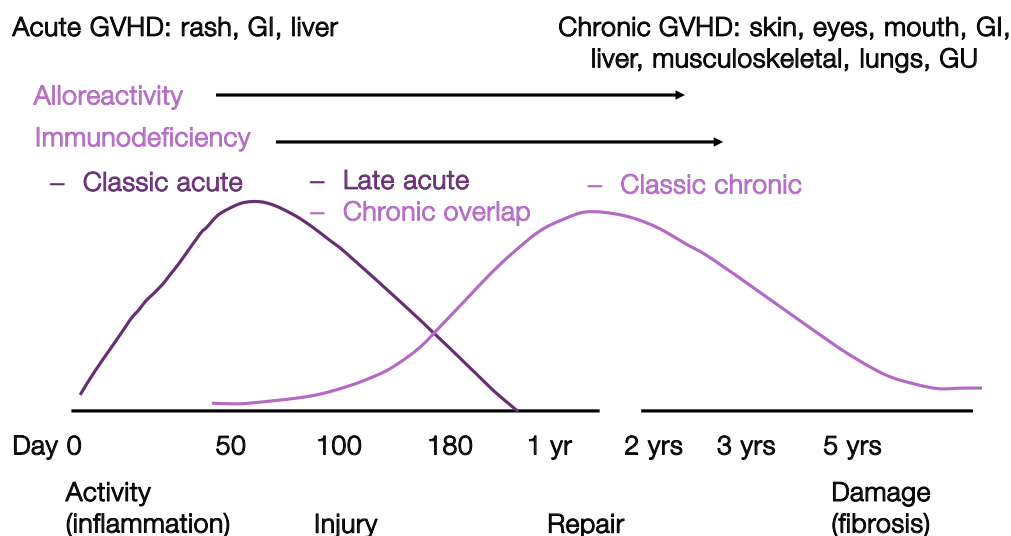
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BACKGROUND

KEY POINT: Two types of GVHD—acute and chronic

- Occurs when immune cells from the donor attack host tissue in the recipient
- Two main types of GVHD, as shown in this post-allogeneic stem cell transplant timeline (Figure 1)
- Acute GVHD (aGVHD), generally within the first 100 days after transplant
 - Mediated almost entirely by alloreactive T-cells that recruit other immune effectors to the site of immunologic attack
- Chronic GVHD (cGVHD), generally after 100 days from transplant
 - More complicated than aGVHD, involving cells of several other lineages, including B-cells and cells of the monocyte-macrophage lineage
- There is also late aGVHD and early cGVHD, which can overlap in patients

Figure 1. GVHD syndrome after allogeneic stem cell transplant.



ACUTE GVHD

KEY POINT: aGVHD affects gastrointestinal tract, liver, and skin only

- Occurs in 30% to 60% of patients who undergo allogeneic stem cell transplant^[1]
- Strong correlation between GVHD and the graft-vs-leukemia effect of transplant
 - Patients with lower rates of GVHD post-transplant usually have higher rates of relapse^[2]
 - Affects 3 organs only: the skin (rash), the GI tract (watery diarrhea), the liver (hyperbilirubinemia)^[3]
 - Staging: Mount Sinai Acute GVHD International Consortium (MAGIC) criteria (Table 1)

Table 1. aGVHD: Staging by MAGIC Criteria^[4]

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	Adult: < 500 mL/day or < 3 ep/day Child: < 10 mL/kg/day or < 4 ep/day
1	Maculopapular rash < 25% body surface area (BSA)	2-3 mg/dL	Persistent nausea, vomiting, or anorexia	Adult: 500-999 mL/day or 3-4 ep/day Child: 10-19.9 mL/kg/day or 4-6 ep/day
2	Maculopapular rash 25% to 50% BSA	3.1-6.0 mg/dL		Adult: 1000-1500 mL/day or 5-7 ep/day Child: 20-30 mL/kg/day or 7-10 ep/day
3	Maculopapular rash > 50% BSA	6.1-15 mg/dL		Adult: > 1500 mL/day or > 7 ep/day Child: > 30 mL/kg/day or > 10 ep/day
4	Generalized erythroderma (> 50% BSA) plus bullous formation and desquamation > 5%	> 15 mg/dL		Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume)

ACUTE GVHD TREATMENT

KEY POINTS: Corticosteroids are the standard treatment for frontline aGVHD; ruxolitinib is the only drug FDA approved for steroid-refractory aGVHD

- Treatment goals:
 - Improve individual organ manifestations
 - Limit treatment-related toxicities of therapies
 - Improve patient's functional capacity and quality of life
 - Improve OS
- Corticosteroids (eg, methylprednisolone, prednisone) are standard of care for frontline aGVHD
- JAK inhibitor ruxolitinib currently the only drug FDA approved for treatment of steroid-refractory aGVHD
 - Approval based on results from the REACH1 study, an open-label, single-arm phase II trial of ruxolitinib plus a corticosteroid in patients 12 years of age or older with grade 2-4 steroid-refractory aGVHD (N = 71)^[5]
 - ORR at Day 28 post ruxolitinib initiation (primary endpoint) ≈ 55% (n = 39); 26.8% (n = 19) with CR (Table 2)
 - Common treatment-related adverse events: anemia (64.8%), thrombocytopenia (62.0%), neutropenia (47.9%), hypokalemia (49.3%), peripheral edema (45.1%)
- Phase II trial with a rheumatoid arthritis drug, abatacept, plus a calcineurin inhibitor and methotrexate has shown promising results as prophylaxis in patients with aGVHD
 - Day 100 post transplant grade 3/4 aGVHD incidence rate: 3% vs 32% (historical controls)^[6]

Table 2. REACH1: Ruxolitinib in Steroid-Refractory aGVHD^[5]

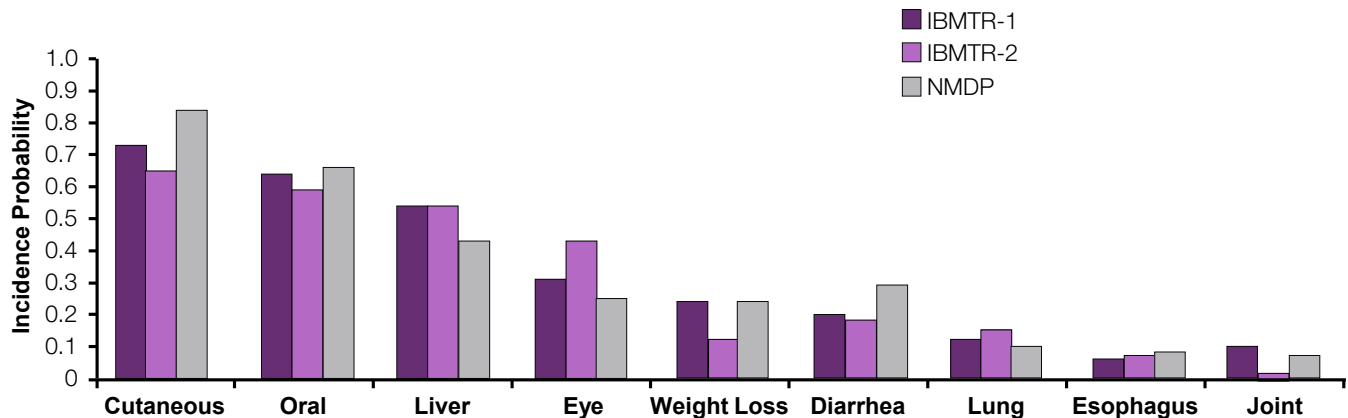
Response at Day 28 by Grade of aGVHD at Enrollment, n (%)	Grade 2 (n = 23)	Grade 3 (n = 34)	Grade 4 (n = 14)	All Patients (N = 71)
ORR	19 (82.6)	14 (41.2)	6 (42.9)	39 (54.9)
• CR	11 (47.8)	7 (20.6)	1 (7.1)	19 (26.8)
• VGPR	4 (17.4)	2 (5.9)	1 (7.1)	7 (9.9)
• PR	4 (17.4)	5 (14.7)	4 (28.6)	13 (18.3)

CHRONIC GVHD

KEY POINT: cGVHD affects eyes, GI tract, genitourinary tract, liver, lungs, mouth, musculoskeletal system, skin

- cGVHD: more complex and involves many more organs than aGVHD, with many additional complications (Figure 2)
 - cGVHD is staged and graded with each organ given a severity score from 1-3 (Table 3)
 - All organ scores are then factored into a composite National Institutes of Health overall category of cGVHD: mild, moderate, and severe, with severe indicating a disability in at least 1 organ system

Figure 2. cGVHD: organ involvement.^[7]



IBMTR, International Bone Marrow Transplant Registry severity index; NMDP, National Marrow Donor Program.

Table 3. cGVHD Assessment^[8,9]

Category	Number of Organs	Maximum Severity
Mild	≤ 2	1 (0 for lung)
Moderate (a)	≥ 3	1 (0 for lung)
Moderate (b)	Any	2 (1 for lung)
Severe	Any	3 (2 for lung)

0: no clinical manifestations/symptoms; 1: clinical manifestations with no more than mild disability; 2: clinical manifestations with moderate disability; 3: clinical manifestations with severe disability

CHRONIC GVHD TREATMENT

KEY POINTS: Corticosteroids are the standard treatment for frontline cGVHD; ibrutinib is the only drug FDA approved for steroid-refractory cGVHD

- Treating newly diagnosed cGVHD is even more challenging than aGVHD management
 - Outcomes for cGVHD are less successful than for aGVHD; up to 80% of patients with cGVHD progress within their first year after initiating frontline therapy
- Reasonable treatment options in combination with corticosteroids include mycophenolate mofetil, tacrolimus, cyclosporine, or extracorporeal photopheresis^[10]
- BTK inhibitor ibrutinib: the only drug FDA approved for treatment of steroid-refractory cGVHD, after progression on ≥ 1 lines of systemic therapy
 - Approval based on results from an open-label phase II trial in patients (N = 42) with steroid-refractory cGVHD (Figure 3)^[11]
 - ORR: 67% (28/42 patients); 9 CR, 19 PR
 - Most common adverse events: fatigue, diarrhea, muscle spasms, nausea, bruising

Figure 3. Ibrutinib in steroid-refractory cGVHD: response (N = 42).^[11]

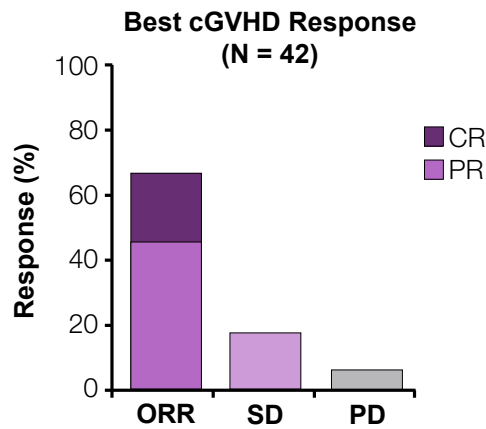


Table 4. Key Ongoing Trials in cGVHD

Trial	Phase	Patient Population	Treatment	Primary Endpoint	Results
iNTEGRATE (NCT02959944)	III	New onset (N = 186)	Ibrutinib + corticosteroids vs placebo + corticosteroids	ORR at 48 weeks	Pending (fully accrued)
REACH3 (NCT03112603)	III	Steroid-refractory (N = 330)	Ruxolitinib vs best available therapy	ORR	Pending (fully accrued)
ROCKstar (NCT03640481)	II	Heavily pretreated (N = 125)	KD025 at either 200 mg QD or 200 mg BID	ORR	ORR 64% (QD), 67% (BID) ^[12] Toxicity: fatigue, diarrhea, nausea most common (all higher with QD dosing)

References

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