HEMATOLOGY BOARD REVIEW MANUAL

Diagnosis and Management of Acute and Chronic Graft-versus-Host Disease

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QUESTIONS

1. A 38-year-old man with high-risk acute myeloid leukemia in second complete remission is eligible to receive a hematopoietic stem cell transplant (HSCT) with full-intensity conditioning. He has a sibling donor selected to provide a bone marrow graft. Which kind of graft-versus-host disease (GVHD) prophylaxis should not be considered in this setting?

A. Cyclosporine + methotrexate
B. Cyclosporine + mycophenolate mofetil (MMF)
C. Antithymocyte globulin (ATG) during conditioning
D. Cyclosporine alone
E. Cyclophosphamide post-transplant

2. A 42-year-old man with acute myeloid leukemia in first complete remission receives a HSCT. The donor is an HLA-matched related donor and GVHD prophylaxis is achieved with MMF and ATG. On day +60 post-transplant, the patient presents with aGVHD of the skin and gastrointestinal tract, which has been clinically diagnosed and confirmed with biopsy. The patient has a moderate response to treatment with steroids and infliximab, with lingering red skin and diarrhea on day +110. A new skin biopsy does not show fibrosis features. How should this patient’s disease be defined?

A. Early cGVHD
B. Refractory aGVHD
C. Overlap syndrome
D. Corticosteroid-refractory aGVHD
E. Extensive cGVHD

3. A 25-year-old woman received a HSCT from a matched related donor for acute myeloid leukemia in first remission. The intensity of conditioning was reduced. Engraftment was observed at day +17 post-transplant. At day +30, she presents with erythema covering less than 25% of body surface area, no fever, no diarrhea, and normal bilirubin level. How should this patient be treated?

A. Local corticosteroids
B. Corticosteroid 0.5 mg/kg/day
C. Corticosteroid 1 mg/kg/day
D. Corticosteroid 1 mg/kg/day + etanercept
E. Corticosteroid 2 mg/kg/day

4. After undergoing a double-unit cord blood transplant, a patient develops grade III GVHD at day +50 after transplant with skin rash and diarrhea. She receives steroids and her symptoms improve, allowing tapering of corticosteroids. At day +110, she is seen with rash involving more than 50% of surface body area and diarrhea of 1 L per day for more than 3 days. Which of the following represents the best approach to treating this patient?

A. Treat as cGVHD and consider extracorporeal photochemotherapy (ECP) with corticosteroids
B. Treat as an aGVHD flare, increase corticosteroid dose, and add a second-line treatment
C. Treat as corticosteroid-refractory aGVHD
D. Treat as cGVHD and consider rituximab
E. Provide symptomatic treatment of diarrhea with rehydration

5. A patient who received a HSCT from a matched unrelated donor for acute lymphoblastic leukemia is seen at day +365 post-transplant. Sclerosis around his waistline is noted and fasciitis of his upper extremities prevents full range of motion. Prednisone is started as cGVHD first-line treatment, but on day +400 the patient reports difficulty swallowing.

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Esophagogastroduodenoscopy (EGD) shows a stricture which is dilated. What is the best treatment option?

A. Stop prednisone and start ECP
B. Continue prednisone and start ECP
C. Continue prednisone and start rituximab
D. Continue prednisone and start sirolimus
E. Items B, C, or D

ANSWERS
1. The correct answer is (C), Antithymocyte globulin (ATG) during conditioning. Although randomized studies have shown reduced rates of acute GVHD (aGVHD) and chronic GVHD (cGVHD) with ATG, these data applied to transplantation from unrelated donors only. More important, in vivo T-cell depletion with ATG has the potential to compromise the antileukemia activity of donor T-cells. Here, the patient has a high risk of relapse since he is in the second remission of high-risk acute myeloid leukemia. So ATG should not be considered as GVHD prophylaxis in order to ensure an efficient allogeneic graft-versus-leukemia effect. Another point to take into account is the source of cells for transplantation: bone marrow is associated with a significantly lower rate of death due to cGVHD compared with peripheral blood stem cells (PBSC; 10% and 21%, respectively, in a recent study from the Blood and Marrow Transplant Clinical Trial Network). Moreover, in this study, the proportion of patients with extensive cGVHD was higher in the PBSC group than in the bone marrow group (48% vs. 32%, P < 0.001). Thus, there is no reason to change the classical GVHD prophylaxis schema including at least a calcineurin inhibitor.

Cyclophosphamide post-transplantation could be an option in centers with experience with that kind of prophylaxis. This prophylaxis has the advantage of using immunosuppressive drugs for a shorter period after transplantation and not impeding graft versus leukemia effect.

References

2. The correct answer is (B), Refractory aGVHD. This patient’s aGVHD was diagnosed at day +60 and has never been controlled. According to the National Institutes of Health consensus document published in 2005, the patient has refractory aGVHD even though he presented beyond day +100 post-transplant. There is no distinctive clinical manifestation corresponding to cGVHD in this case. The diagnosis of overlap syndrome might be confusing, but the biopsy performed at day +110 allows the elimination of cGVHD subclinical features.

Reference

3. The correct answer is (A), Local corticosteroids. As with the patient described in this case, the first clinical manifestation of aGVHD in most recipients is a maculopapular rash. These patients are not likely to require systemic treatment, and topical steroids are the most commonly used skin-directed therapy for this low-grade aGVHD. Antihistamines may be used as adjuvant therapy for patients with pruritus. The recommendations are to optimize the cyclosporine level given as GVHD prophylaxis concurrently with local corticosteroids. As in systemic therapy, a flare effect might be observed after tapering topical corticosteroids.

Patients with aGVHD requiring systemic therapy (grades II–IV) are typically started on methylprednisolone or a prednisone equivalent at a dose of
2 mg/kg/day (divided in 2 doses). Based on a retrospective study assessing low-dose prednisone in aGVHD, some centers begin treatment with methylprednisolone-equivalent doses of 1 mg/kg/day in patients with milder (grade II) aGVHD, with dose escalation to 2 mg/kg/day if patients exhibit progressing GVHD after 3 days of therapy.2,4

Etanercept can be considered in refractory aGVHD, but should not be included in first-line treatment.2,5

References

4. The correct answer is (B), Treat as an aGVHD flare, increase corticosteroid dose, and add a second-line treatment. Gradual corticosteroid tapering is important to prevent a flare of GVHD. Nevertheless, it does not systematically prevent it. The patient in this case presents with aGVHD with flare effect when tapering corticosteroids. The time onset beyond day +100 post-transplant is not sufficient to evoke a diagnosis of cGVHD.1 The recommendations are to increase corticosteroids to 2 mg/kg/day and to add a second-line treatment. ECP and rituximab are not appropriate here as they are second-line treatments for cGVHD.2,4

Providing symptomatic treatment of diarrhea with rehydration is not the correct approach because the patient presented with grade III aGVHD. Severity of aGVHD and absence of response to corticosteroids are associated with higher mortality.

References

5. The correct answer is (E), Items B, C, or D. Approximately 50% of patients with cGVHD fail to achieve control after initial therapy with steroids by 1 year after diagnosis.1 There is currently no standard of care for cGVHD patients in whom frontline steroid-based therapy fails, so enrollment in a clinical trial is recommended. All recommendations beyond steroids are based on phase 2 studies, and most of them report response rates varying from 25% to 80% and 1- to 3-year survival rates of approximately 70%. ECP and rituximab are the most promising approaches in current published data in this setting.2,4 Whichever treatment is selected, systemic prednisone should be administered in combination with the second-line treatment.

References