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Guideline

Guidelines for the Prevention and Management of Graft-versus-Host Disease after Cord Blood Transplantation

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A B S T R A C T

The incidence of graft-versus-host disease (GVHD) after cord blood (CB) transplantation (CBT) is lower than expected given the marked degree of human leukocyte antigen (HLA)-mismatch of CB grafts. While the exact mechanism that underlies this biology remains unclear, it is hypothesized to be due to the low number of mostly immature T-cells infused as part of the graft1,2, and increased tolerance of CB-derived lymphocytes induced by the state of pregnancy. Nevertheless, acute GVHD (aGVHD) is a significant complication of CBT. In contrast, the incidence of chronic GVHD (cGVHD) following CBT is lower than what is observed following matched related or unrelated donor HSC transplantation (HSCT)3-6. This review outlines the guidelines for the prevention and management of acute and chronic GVHD following CBT.

INTRODUCTION

The incidence of graft-versus-host disease (GVHD) after cord blood (CB) transplantation (CBT) is lower than expected given the marked degree of HLA mismatch of CB grafts. Although the exact mechanism that underlies this biology remains unclear, it is hypothesized to be due to the low number of mostly immature T cells infused as part of the graft [1,2], and increased tolerance of CB-derived lymphocytes induced by the state of pregnancy. Nevertheless, acute GVHD (aGVHD) is a significant complication of CBT. In contrast, the incidence of chronic GVHD (cGVHD) following CBT is lower than that seen following matched related or unrelated donor HSC transplantation (HSCT) [3-6]. This review outlines the guidelines for the prevention and management of aGVHD and cGVHD following CBT.

FAQ1: HOW DOES GVHD PROPHYLAXIS AND MANAGEMENT FOLLOWING CBT DIFFER FROM ADULT DONOR GRAFT SOURCES?

The major difference in GVHD prophylaxis following CBT is the general avoidance of methotrexate (MTX) owing to its negative impact on hematopoietic recovery [7-9]. In addition, the feasibility of GVHD prophylaxis with post-transplantation cyclophosphamide (PTCy) remains to be confirmed [10]. By contrast, the management of aGVHD and cGVHD following CBT and adult donor transplantation are broadly similar. However, aGVHD and cGVHD after CBT have been associated with greater responsiveness to first-line treatment with corticosteroids [11-15].

FAQ2: IS PRE-ENGRAFTMENT SYNDROME (PES) DISTINCT FROM AGVHD?

Yes. PES is considered distinct from aGVHD and is defined as unexplained fever and/or erythematous rash occurring before hematopoietic recovery in the absence of a documented infection [16]. PES also may be associated with fluid overload, renal, pulmonary, and gastrointestinal (GI) manifestations [16-22]. The incidence of PES after CBT varies from 20% to 87% and

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Table 1
GVHD Prophylaxis in CBT

Drug	Dose	Therapeutic Goal/Comments
Cyclosporine* (Neoral)	Adults: 3 mg/kg IVPB every 12 intravenous over 2 h starting on day -3 Actual body weight	Therapeutic range, 275-350 ng/mL. The i.v. to p.o. conversion is 1:1-1.5 if on azole; all others, 1:3.
Tacrolimus* (Prograf)	Adults: 0.02 mg/kg/day continuous infusion intravenous over 24 h starting on day -3; 0.015 mg/kg for patients age >70 yr Actual body weight	Therapeutic range, 6-12 ng/mL. The i.v. to p.o. conversion is 1:3.
Mycophenolate mofetil (MMF) (Cellcept)	Adults: 15 mg/kg i.v. every 8 h starting pretransplantation; maximum 1500 mg every 8 h	The i.v. to p.o. conversion is 1:1. Myfortic 180 mg is equivalent to MMF 250 mg.

* Obtain daily CNI levels on day -1 to day +3, then frequently early post-transplantation, especially if with renal and/or hepatic organ dysfunction or when initiating interacting medications or nephrotoxins.

occurs at a median of 7 to 14 days post-CBT [16,17,19-25]. By contrast, the median onset of aGVHD is 36 to 40 days (range, 14 to 169 days) post-transplantation [12,26]. The diagnosis of PES is clinical and can be distinguished from other transplantation complications based on the typical timing of symptom onset and treatment response. Whether PES predisposes to subsequent development of aGVHD is controversial [16,19-21,23,24]. A high response rate has been reported with a short course of i.v. corticosteroids, such as 1 mg/kg for 3 days [16,17]. A minority of patients who experience persistent or recurrent PES manifestations may require an extended course or a second course of corticosteroids.

FAQ3: WHAT IS THE MOST COMMONLY USED GVHD PROPHYLAXIS IN CBT?

In the United States and Europe, the most commonly used GVHD prophylaxis regimen is a calcineurin inhibitor (CNI), such as cyclosporin-A (CSA) or tacrolimus, plus mycophenolate mofetil (MMF) [6] (Table 1). A higher early post-transplantation CNI concentration in HCT or CBT recipients has been associated with reduced aGVHD risk [27-29]; therefore, close monitoring with appropriate dose adjustment to ensure therapeutic CNI levels early post-transplantation is important [28]. Two analyses have identified MMF dose as a critical determinant of aGVHD risk after CBT and support intensified MMF dosing as the standard in MMF-based CBT [30,31].

FAQ4: ARE THERE OTHER GVHD PROPHYLAXIS REGIMENS AFTER CBT?

Less widely used GVHD prophylaxis regimens include the following:

- Tacrolimus and sirolimus combined with antithymocyte globulin (ATG) after reduced-intensity conditioning has been associated with a low cumulative incidence of grade II-IV aGVHD of 9.4% but with slow immune reconstitution and a 2-year progression-free survival of 31% [32].
- General incorporation of ATG into a variety of prophylaxis regimens has similarly been associated with greater risk of infection, delayed immune reconstitution, and increased transplantation-related mortality [32-37]. Therefore, ATG is not recommended as GVHD prophylaxis in CBT recipients.
- In one study, tacrolimus plus sirolimus (without ATG) was associated with a 27% rate of grade II-IV aGVHD and a 17% rate of grade III-IV aGVHD [38].
- Sirolimus plus MMF is a potential CNI-free GVHD prophylaxis regimen but is not yet widely established [39].
- CNI plus MTX at various dosage regimens is most commonly used in Japan. Although effective in mitigating aGVHD risk, MTX use in CBT has been associated with delayed engraftment, especially at higher doses [7-9].
- PTCy use after CBT should be considered experimental at this time [10].

FAQ5: WHAT IS THE INCIDENCE OF AGVHD IN CBT RECIPIENTS?

In children, the reported incidence of day 100 grade II-IV aGVHD is 30% to 60% and that of grade III-IV aGVHD is 15% to 30% [40-42]. In adults, the day 100 incidences of grade II-IV and grade III-IV aGVHD are 30% to 60% and 20% to 30%, respectively. How these rates compare to those with other graft sources is influenced by multiple factors, including graft type (peripheral blood stem cell [PBSC] versus bone marrow), donor-recipient HLA match, and type of GVHD prophylaxis, including *ex vivo* or *in vivo* T cell depletion [3,5,43,45–50]. Notably, a lower incidence of aGVHD has been reported in CBT recipients compared with unmodified allele-matched PBSC allograft recipients [44].

FAQ6: DOES THE INCIDENCE OF AGVHD DIFFER AFTER SINGLE-UNIT CBT COMPARED TO DOUBLE-UNIT CBT (DCBT)?

There are conflicting data surrounding this question [41,51,52]. However, the consensus is that aGVHD incidence is increased after double-unit CBT (dCBT). Single-unit CBT has been associated with a 20% to 40% incidence of grade II-IV aGVHD and a 7% to 10% incidence of grade III-IV aGVHD [6,26,41,42,53,54]. dCBT has been associated with a 30% to 65% incidence of grade II-IV aGVHD and a 20% to 35% incidence of grade III-IV aGVHD [6,12,41,43,54,55]. A retrospective analysis comparing single-unit CBT to dCBT showed that the latter was associated higher incidence of grade II-IV aGVHD. This difference was due primarily to an increased risk of grade II disease only, predominantly affecting the skin, whereas the incidence of grade III-IV aGVHD was not different [26]. Other studies have shown an increased incidence of grade III-IV aGVHD after dCBT, however [41,54].

FAQ7: DOES BETTER DONOR-RECIPIENT HLA MATCHING DECREASE THE RISK OF AGVHD?

Early data demonstrated a lower incidence of aGVHD with units that are matched to the recipient at 6/6 HLA-A and -B antigens and -DRB1 alleles [40,53,56]. More recent studies using HLA-allele matching have shown a lower rate of grade II-IV aGVHD with 8/8 HLA allele (HLA -A, -B, -C, -DRB1)-matched grafts [57] and a lower rate of grade III-IV aGVHD after dCBT if the engrafting unit is 5-6/6 (HLA-A, -B, -DRB1) allele matched [12]. However, the degree of 8- or 10-allele HLA mismatch might not predict aGVHD severity [12,57-60]. Notably, numerous factors may affect the impact of HLA

mismatch on GVHD incidence and severity including recipient age, conditioning intensity, single- or double-unit graft, use of ATG, distribution of the mismatches within the study population, locus-specific HLA mismatch and graft manipulation [6,26,35,41,53-55,57,61,62]. Therefore, a specific recommendation to optimize HLA-match grade to potentially mitigate severe GVHD cannot be made, especially given that graft cell dose also must be considered.

FAQ8: WHAT ARE OTHER AGVHD RISK FACTORS BEYOND HLA MATCHING AFTER CBT?

Myeloablative conditioning [6,54,63] and absence of ATG [6,26,35,54,55] are the most frequently identified additional risk factors, although one series reported nonmyeloablative conditioning as a risk factor [26]. In addition, age ≥18 years has been identified as a risk factor after single-unit CBT [54]. No associations between diagnosis, patient ancestry, and recipient cytomegalovirus status have been identified [6,12].

FAQ9: WHAT ARE THE TARGET ORGANS MOST FREQUENTLY AFFECTED BY AGVHD AFTER CBT?

The skin is the organ most frequently affected by aGVHD [15,26], whereas the liver is the organ least frequently affected [12,15,26,58]. Other series have reported the combination of skin/GI tract and GI tract alone as frequently affected organs [12,58].

FAQ10: HOW SHOULD AGVHD BE TREATED AFTER CBT?

Upfront therapy of aGVHD after CBT with prednisone (or i.v. equivalent) is no different from other graft sources and should be initiated promptly at the time of clinical diagnosis. Treatment should not be delayed while waiting for pathologic confirmation. The treatment dose is 0.5 to 2 mg/kg based on organ involvement and severity (Figure 1). Lower GI aGVHD after CBT is potentially life-threatening, and any CBT recipient with diarrhea must be promptly evaluated and treated. Patients with diarrhea and a negative infectious workup require systemic corticosteroids. In addition, the presence of *Clostridium difficile* and/or viral infection does not exclude concurrent aGVHD. Higher treatment responses have been reported in pediatric and adult CBT recipients [12-15], although approximately 20% of patients will not respond to upfront therapy [12].

FAQ11: WHEN CAN CORTICOSTEROIDS BE TAPERED IN CBT RECIPIENTS WITH AGVHD?

Corticosteroids taper can be initiated if complete or partial response has been achieved, and as soon as 5 to 7 days after the start of treatment. The duration of the steroid taper is dependent on the severity and responsiveness of the GVHD.

FAQ12: WHAT IS THE INCIDENCE OF CORTICOSTEROID-REFRACTORY AGVHD FOLLOWING CBT?

Steroid refractoriness or resistance is defined as progression of aGVHD within 3 to 5 days of therapy onset with 2 mg/kg/day of prednisone (or i.v. equivalent), or failure to improve within 5 to 7 days of treatment, or incomplete response after more than 28 days of immunosuppression treatment including corticosteroids. Approximately 20% of CBT recipients with aGVHD do not respond to upfront corticosteroid therapy [12]. In adults and children age ≥12 years, the only Food and Drug Administration-approved second line of therapy is the Janus-associated kinase inhibitor ruxolitinib [64]. Dosage adjustment for drug interactions or bone marrow suppression may be required.

FAQ13: WHAT IS THE INCIDENCE OF CGVHD AFTER CBT?

This has varied, but when defined by National Institutes of Health criteria [65], the incidence of cGVHD is low relative to that after adult PBSC transplantation, and when it occurs, it is usually mild or moderate [12,66]. Thus, 2- to 3-year cumulative cGVHD incidence rates of 7% to 23% have been reported [4,5,12,58]. The median time of onset of cGVHD is 210 to 233 days (range, 83 to 803 days) [5,12]. Notably, GVHD occurring beyond day 100 post-CBT commonly presents with acute manifestations, in the form of either persistent/recurrent aGVHD or late-onset aGVHD, or overlap cGVHD syndrome, whereas classic cGVHD is rare [12,67-69].

FAQ14: WHAT ARE THE RISK FACTORS FOR CGVHD AFTER CBT?

Like other stem cell sources, after CBT, the probability of developing cGVHD is higher in patients with previous aGVHD [26,54,66]. The use of double-unit grafts has been associated

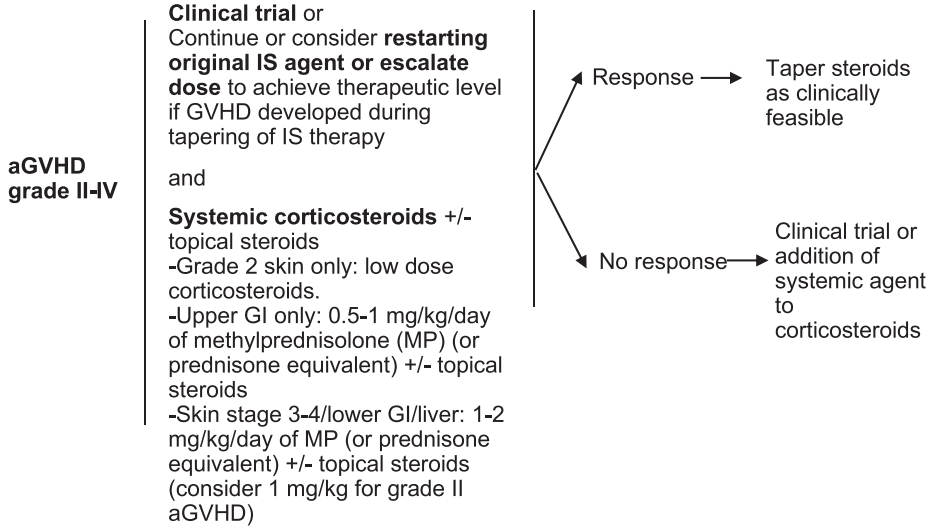

Figure 1. Treatment of grade II-IV aGVHD.

with a higher incidence of extensive cGVHD [42,52]. The degree of HLA mismatch and use of serotherapy have not been associated with cGVHD risk after CBT [6,54,59,70].

FAQ15: WHAT ORGANS ARE MOST COMMONLY AFFECTED BY CGVHD AFTER CBT?

cGVHD after CBT is usually limited to mucocutaneous involvement [12,66,69]. The skin is the most frequently affected organ, followed by mild ocular and oral involvement. In contrast to other stem cell sources, severe ocular, sclerotic skin involvement, contractures, and symptomatic pulmonary involvement are rare [12,69].

FAQ16: HOW IS CGVHD AFTER CBT TREATED?

Management of cGVHD after CBT does not differ from that after transplantation with other stem cell sources, with 0.5 to 1 mg/kg/day of prednisone (or i.v. equivalent) added for upfront therapy for moderate to severe cGVHD. Topical steroids may be used for mild skin cGVHD or as ancillary therapy for moderate/severe cGVHD. In the context of cGVHD primary therapy, steroid-sparing therapy is either not used or, more commonly, begins with a CNI or sirolimus. At present, ibrutinib is the only approved agent for patients with cGVHD after failure of one or more previous therapies [71]. cGVHD treatment response is higher following CBT compared with after unrelated adult donor allogeneic transplantation [11].

FAQ17: IN THE ABSENCE OF GVHD, WHEN CAN IMMUNOSUPPRESSION BE TAPERED IN CBT RECIPIENTS?

Immunosuppression tapering after CBT has not been well studied, and the practice varies among centers. CNI taper can be initiated at 3 to 6 months post-CBT in the absence of GVHD. Centers may use disease risk, toxicity and complications of immunosuppressive therapy, and degree of donor-recipient HLA match as factors to determine the timing and speed of taper. Immunosuppression taper should be held in the setting of active GVHD. The speed of MMF taper is controversial. Some centers discontinue MMF without taper at days 30 to 45 post-CBT (or at 7 days postengraftment if beyond day 30) in the absence of aGVHD. Others taper MMF beginning on days 30 to 45 in 10% to 25% decrements, with the aim of being off drug by day 100. In patients at high risk of relapse or with early disease relapse or progression, early taper or cessation of MMF can be considered, with close observation for aGVHD. In patients who are intolerant of CNI, MMF taper may be delayed, permitting taper of CNI beforehand.

FAQ18: HOW DOES GVHD IMPACT CBT OUTCOMES?

The data are conflicting [6,54,72,73]. Grade II aGVHD has been associated with a reduced risk of relapse and either a favorable effect or no adverse effect on overall mortality [6,72]. Although grade III-IV aGVHD also has been associated with reduced relapse risk, this benefit is offset by increased transplantation-related mortality and inferior survival [6,54,72,73]. Most studies have found survival to be either improved or unaffected by cGVHD [6,54,68,72,74]. Consistent with the lower severity of GVHD post-CBT and high response to treatment overall, CBT recipients achieve a high rate of immunosuppression discontinuation, have a low burden of disabilities related to cGVHD, and enjoy an improved quality of life [67,69,75].

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