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REVIEW

Acute graft-versus-host disease in children

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Acute graft-versus-host disease (GVHD) is one of the major complications of hematopoietic stem cell transplantation. Many variables including stem cell source, age of donor and recipient, preparative regimen and prophylaxis can impact the likelihood and severity of GVHD. The major portion of this review concentrates on risk factors, treatment and outcome, since here we may see differences between children and adults. Pathophysiology and manifestations/grading of acute GVHD are also briefly presented. An effort has been made to concentrate either on pediatric trials or look specifically at the pediatric subset of larger studies.
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Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative option in children with high-risk malignancies such as acute lymphoblastic leukemia and acute myeloid leukemia. Furthermore, HSCT has been employed to cure children of certain non-malignant conditions such as severe combined immunodeficiency and sickle-cell disease. Because transplant carries a significant risk of morbidity and mortality, the decision to proceed with HSCT must carefully balance risks and benefits. One of the major risks is acute graft-versus-host disease (GVHD). GVHD occurs after recognition of host tissues from the donor immune system. Children are at less risk for GVHD than adults; however, that risk is still significant especially when using alternative donor sources. In this review, pathophysiology, manifestations and grading, risk factors for acute GVHD, treatment options (including prophylaxis) and outcome are presented. One of the major aims is to review acute GVHD specifically in the context of pediatric stem cell transplantation.

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Pathophysiology of acute GVHD

The pathophysiology of acute GVHD has been described by Ferrara and co-workers as a three-phase phenomenon (see diagrammatic representation in Figure 1). The first phase involves damage to host tissues by inflammation from the preparative chemo- and/or radiotherapy regimen. In the second phase, both recipient and donor antigen-presenting cells, as well as inflammatory cytokines trigger activation of donor-derived T cells, which expand and differentiate into effector cells.[1] In this activation phase, minor histocompatibility antigens play a central role particularly in the setting of matched sibling transplants. Much of the initial inflammatory cascade is thought to begin in the gastrointestinal (GI) tract, and patients with higher volumes of diarrhea at the time of the preparative regimen have a higher likelihood of acute GVHD.[2]

T-cell activation pathways result in the transcription of genes for cytokines, such as interleukin-2 and interferon. T cells that produce interleukin-2, and interferons are considered to be of the Th1 phenotype. In the third (effector) phase, activated donor T cells mediate cytotoxicity against target host cells through Fas–Fas ligand interactions, perforin–granzyme B and the additional production of cytokines such as tumor necrosis factor-α (TNF-α). TNF-α is produced mainly by monocytes and macrophages. TNF-α has been implicated in the pathophysiology of GVHD at several steps in the process, including induction of apoptosis in target tissues through the TNF-α receptor; activation of macrophages, neutrophils, eosinophils, B cells and T cells; stimulating the production of additional inflammatory cytokines; increased expression of human leukocyte antigen (HLA) and facilitation of T-lymphocyte lysis. This allogeneic interaction in the setting of cytokine dysregulation leads to the tissue damage characteristic of acute GVHD.[1,3]

Manifestations and grading

Acute GVHD is staged by the number and extent of organ involvement. The current staging system was devised by Glucksberg in 1974, and then modified at the Keystone Conference in 1994 (Table 1).[4] Recent data support the use of the grading system, since it is able to subdivide patients into risk categories for complications and mortality.[5]

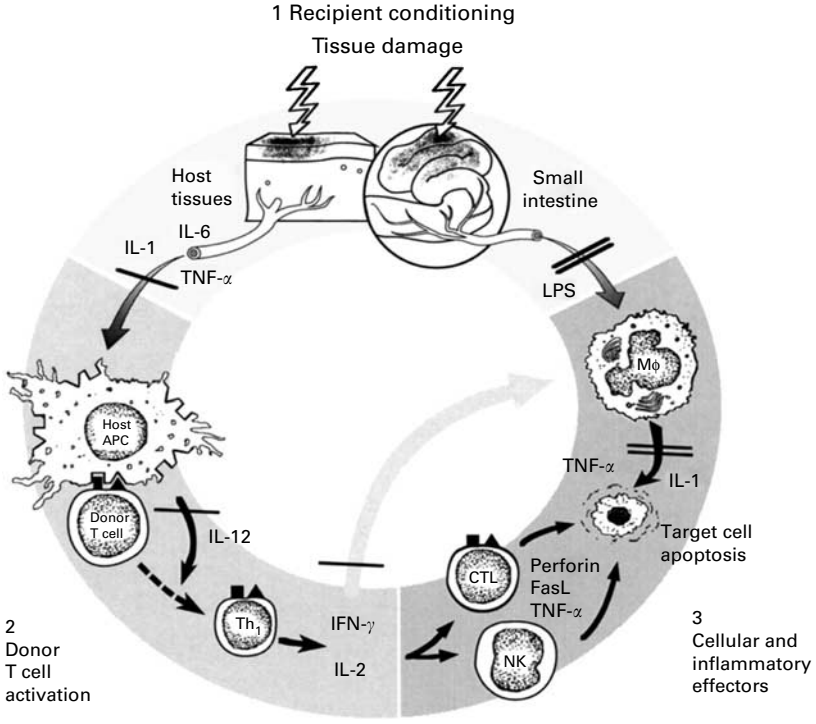

Figure 1 Acute GVHD pathophysiology—the three sequential phases of GVHD are detailed. (taken from Hill and Ferrara[1]. Copyright American Society of Hematology, used by permission). GVHD, graft-versus-host disease.

Although staging of gut GVHD for pediatric patients was not discussed at the Conference, most pediatric centers have defined staging of gut GVHD based on volume per kilogram of body weight as opposed to absolute volume of diarrhea.

The diagnosis is suspected when a recipient of HSCT develops any or all of the following signs or symptoms: dermatitis (skin rash); cutaneous blisters; crampy abdominal pain with or without diarrhea; persistent nausea and vomiting and hepatitis (with elevation of bilirubin and/or liver enzymes). Typically these symptoms occur before day 100 after the HSCT—with donor engraftment—but may occur later. Acute GVHD is a clinical diagnosis, but as many of the symptoms of acute GVHD are non-specific, histologic confirmation, especially if the symptoms are atypical or involve just the liver or gut, may be extremely useful.

Risk factors for acute GVHD

The risk factors for acute GVHD are well defined. The most important factor is HLA disparity. Table 2 lists a variety of different pediatric studies with the incidence and severity of acute GVHD. Among siblings, patients receiving matched grafts have lower rates of GVHD than those receiving HLA-mismatched grafts. In a large registry-based study of allogeneic matched-sibling bone marrow transplants (630 children with leukemia), the incidences of grade II–IV and grade III–IV acute GVHD were 28 and 11%, respectively.[6]

For unrelated donor transplants, greater the degree of HLA mismatch, the higher the likelihood of developing acute GVHD and the worse the overall outcome. Recent data from the National Marrow Donor Program suggest that allele level matching (high resolution) as opposed to group matching (low-resolution) provides advantage in reducing the likelihood of GVHD.[7] We have observed the same trends in pediatric GVHD. Up to the late 1990s, the approach was to match at HLA-A and B at the group level, and at HLA-DRB1 at the allele level. Using this approach with unmanipulated unrelated bone marrow led to an incidence of severe acute GVHD (grade III/IV) in the 30–50% range in children.[8,9] Prospective high-resolution matching of unrelated donors at 10 alleles (HLA-A, -B, -C, -DRB1 and -DQB1) led to grade III/IV GVHD incidence of 8% in a recently reported Italian study. Of the 63 patients, 59 received unrelated donor bone marrow and four received peripheral blood stem cells. The majority of grafts were matched at 9–10/10 alleles.[10] The 8% incidence of severe acute GVHD is remarkably low for unrelated donor transplants, and although the high degree of matching may explain these results, one must also bear in mind this was a fairly small study and so results may not be completely generalizable.

As for the source of the graft, unrelated cord blood has become an important alternative stem cell source, particularly in children. The immunologic naiveté of these cells allows for greater degrees of mismatch, and in a single-institution study recipients of mismatched (4/6 or 5/6 HLA group match) unrelated cord blood, appear to have similar incidence of acute GVHD and similar overall outcome as

Table 1 Extent of organ involvement

Stage	*Skin*	*Liver (bilirubin)*	*Gut (stool output per day)*
0	No GVHD rash	<2 mg/dl	<500 ml/day or persistent nausea (child: <10 ml/kg/day)
1	Maculopapular rash <25% BSA	2–3 mg/dl	500–999 ml/day (child: 10–19.9 ml/kg/day) or persistent nausea, vomiting or anorexia, with a positive upper GI biopsy
2	Maculopapular rash 25–50% BSA	3.1–6 mg/dl	1000–1500 ml/day (child: 20–30 ml/kg/day)
3	Maculopapular rash >50% BSA	6.1–15 mg/dl	Adult: >1500 ml/day (child: >30 ml/kg/day)
4	Generalized erythroderma plus bullous formation	>15 mg/dl	Severe abdominal pain with or without ileus
Grade			
I	Stages 1–2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	—	Stages 2–3 or	Stages 2–4
IV	Stage 4 or	Stage 4	—

Abbreviations: BSA = body surface area; GI = gastrointestinal; GVHD = graft-versus-host disease.

Table 2 Incidence of acute GVHD in pediatric studies

	Acute GVHD grade II–IV (%)	*Acute GVHD grade III–IV (%)*	*No. of patients, reference*
HLA-identical sibling, bone marrow	28	11	$N=630$, Eapen *et al.*[6] Multi-institution, registry
HLA-identical sibling, peripheral blood	27	13	$N=143$, Eapen *et al.*[6] Multi-institution, registry
Unrelated donor, bone marrow (six-antigen low-resolution typing), 64% 6/6 matches	85	49	$N=88$, Woolfrey *et al.*[8] Single institution
Unrelated donor, bone marrow (low-resolution A and B, high-resolution DRB1 typing), 80% 6/6 matches	56	30	$N=262$, Rocha *et al.*[9] Multi-institution
Unrelated donor, bone marrow (high-resolution 10 allele typing), 48% 10/10 matches	40	8	$N=63$, Giebel *et al.*[10] Two centers
T-cell-depleted, unrelated donor, bone marrow (low-resolution A and B, high-resolution DRB1 typing), 54% 6/6 matches	19	8	$N=180$, Rocha *et al.*[9] Multi-institution
Unrelated cord blood (low-resolution A and B, high-resolution DRB1 typing), 8% 6/6 matches	33	22	$N=99$, Rocha *et al.*[9] Multi-institution
Unrelated cord blood (low-resolution A and B, high-resolution DRB1 typing), 15% 6/6 matches	19	11	$N=26$, Jacobsohn *et al.*[11] Single institution
Unrelated cord blood (low-resolution A and B, high-resolution DRB1 typing), 9% 6/6 matches	41	31	$N=32$, Wall *et al.*[12] Multi-institution

Abbreviations: GVHD = graft-versus-host disease; HLA = human leukocyte antigen.

compared with matched-sibling transplants.[11] The multi-institutional pediatric leukemia transplant study by the Cord Blood Transplantation group reported a grade II–IV acute GVHD incidence of 41% in 32 recipients of 4–6/6 HLA unrelated cord blood transplants.[12] This acute GVHD incidence is closer to what is reported in unrelated donor transplants. Interestingly, when the group retrospectively performed high-resolution HLA typing, 13 of 30 recipients were reclassified with a lesser match than at the original low-resolution typing. Patients with a high-resolution 3/6 or 4/6 HLA match had lower survival than 5–6/6 patients. Incidence of acute GVHD specifically was not looked at by the degree of high-resolution typing. Although the numbers are small, there is a suggestion that high-resolution HLA matching may play a role in unrelated cord blood (UCB) transplants.

There is increasing use of peripheral blood stem cells (PBSCs) as a way of collecting cells from related or unrelated donors. No randomized study has been completed to determine if PBSC transplants change GVHD incidence or the eventual outcome. However, there is a suggestion from a meta-analysis that acute GVHD is slightly increased (relative risk 1.16, $P=0.006$) and chronic GVHD is increased (relative risk 1.53, $P<0.001$) when comparing PBSC and bone marrow transplants.[13] There are few reports of acute GVHD following PBSC transplants in pediatrics. Eapen recently reported a similar incidence of grade II–IV and grade III–IV acute GVHD in PBSC ($N=143$) as compared with bone marrow transplants ($N=630$) in a large, retrospective registry study of pediatric leukemia patients. Incidence of grade II–IV acute GVHD was 27 and 28%, and of grade III–IV acute GVHD was 13 and 11%, for PBSC and bone marrow transplant recipients, respectively. There was decreased overall survival (primarily from increased transplant-related mortality) in the group that received PBSC allografts; however, that

may reflect a higher-risk nature of those patients, since 22% of PBSC patients were in relapse/primary induction failure as opposed to 11% of the bone marrow recipients.[6]

Other factors can also increase the likelihood of acute GVHD. Older age of both recipient and donor increases the probability of GVHD. Sex mismatch, specifically a multiparous female donor into a male patient, increases the likelihood of GVHD. A malignant as opposed to non-malignant diagnosis leads to more GVHD. Furthermore, because of increased tissue damage, the intensity of the preparative regimen does appear to correlate with more acute GVHD. Higher doses of radiation give rise to more GVHD,[14] and the more recent use of non-myeloablative preparative regimens has led to lower incidence of acute GVHD in some studies.[15] While most of these data come from adult studies, it appears that at least two particular factors play a role in an increased rate of acute GVHD in pediatrics: older donor age[16,17] and female donor sex.[16] On the basis of available data it is reasonable to select the best matched donor first, as HLA mismatch is the greatest predictor for GVHD. Other non-HLA factors that would next play a role in selecting a donor would be age (younger) and gender (male). Finally, ABO blood type (compatible) and cytomegalovirus (CMV) serostatus (negative for negative donor) are the last factors that should be examined.

Treatment

For the GVHD treatment approach, please refer to Table 3. The major emphasis in GVHD has been on prevention, as results with treatment have been disappointing. Currently most centers use a combination of a calcineurin inhibitor (cyclosporine or tacrolimus) with short-course methotrexate (MTX). Although other regimens are being explored, this particular regimen has been shown repeatedly to result in a reasonable balance of GVHD and graft-versus-tumor in matched sibling transplants after ablative chemotherapy.[18] In a recently completed prospective unrelated donor transplant study in pediatrics, the incidence of grade III/IV acute GVHD was equivalent when using cyclosporine or tacrolimus for prophylaxis (about 20%).[19] Furthermore, it has been found that in children, having a mean trough concentration below 85 ng/ml in the first 2 weeks post-HSCT increases the risk of acute GVHD in both sibling and unrelated donor transplants.[17] Interestingly, a randomized study comparing low-dose (1 mg/kg/day) versus conventional (3 mg/kg/day) intravenous cyclosporine as GVHD prophylaxis in children undergoing matched-sibling transplants for ALL showed decreased relapse and improved event-free survival in those that received low-dose cyclosporine (CSA).[20] Less relapse was observed in patients with chronic GVHD, presumably through a graft-versus-leukemia effect.

Because of the concern of further delaying engraftment with MTX in unrelated cord blood transplants, many centers have used methylprednisolone along with CSA for prophylaxis. However, time to engraftment was actually similar in the Cord Blood Transplantation study[12] using CSA/methylprednisolone, as compared with unrelated cord blood transplant recipients that received CSA/MTX.[11] Another MTX-sparing regimen that appears to be effective, particularly in unrelated cord blood transplants, is the combination of calcineurin inhibitor and mycophenolate mofetil. In a recent pilot study using FK506/mycophenolate mofetil in pediatrics, investigators showed that this regimen was most effective in GVHD reduction when specifically targeting mycophenolate mofetil levels before day +30.[21]

While many centers have used anti-thymocyte globulin pre-transplant (host immunosuppression) or post-transplant (*in vivo* T-cell depletion) in unrelated or mismatched transplants, there has been a growing experience using alemtuzumab as an alternative, in children. Alemtuzumab is a humanized monoclonal antibody to CD52. One of the concerns is the high potential for infection. By replacing pre- and post-transplant anti-thymocyte globulin with alemtuzumab in children receiving myeloablative mismatched-related or unrelated transplants, the group at Children's Hospital of Los Angeles decreased their incidence of grade III/IV GVHD from 46% to 0. Although this is a retrospective comparison and the numbers are small to draw definitive conclusions, the rate of fungal and viral infections and the rate of relapse were similar in both groups. Survival was also not statistically different.[22] This drug has also been used successfully to promote engraftment and reduce GVHD in combination with a reduced-intensity regimen in children with non-malignant disorders, although with significant early infections.[23]

Once GVHD occurs, centers treat grade II–IV acute GVHD by continuing prophylactic immunosuppression and adding methylprednisolone at 2 or 2.5 mg/kg/day. Steroids are tapered after control of GVHD. In a randomized study looking at different starting steroid doses, patients receiving 2 and 10 mg/kg/day had the same rate of response (70%) and the same 3-year actuarial survival (62%). Higher morbidity was observed with the higher dose.[24] Therefore there appears to be no benefit in using doses higher than 2 mg/kg/day.

Patients not responding to corticosteroids after 5–7 days are treated with salvage therapy. Anti-thymocyte globulin has been used and produces objective responses. However, the long-term survival of patients treated with anti-thymocyte globulin is low (median survival 4.1 months), given the severe immunosuppression and high incidence of infection.[25] There are a number of other approaches under investigation. Some of these include extracorporeal photopheresis (ECP), pentostatin, sirolimus, monoclonal antibodies and mesenchymal stem cells. Well-designed, prospective clinical trials of dosing and timing of various salvage agents are necessary. A number of these agents produce responses; however, infectious mortality remains high.

For example, of 22 heavily treated patients with steroid-refractory acute GVHD treated with pentostatin (an irreversible inhibitor of adenosine-deaminase) on a phase I trial, 17 had an objective response. Unfortunately, five patients who responded, died from late infections either viral or fungal. The survival at 1 year was 25%.[26] It is possible that employing salvage approaches earlier in the process of acute GVHD process may produce an improved

Table 3 Approaches to post-HSCT GVHD prophylaxis and treatment in children

GVHD prophylaxis agents and mechanism of action		
Cyclosporine	Calcineurin inhibitor → blockade of T-cell activation	
FK506	Calcineurin inhibitor → blockade of T-cell activation	
Methotrexate	Antimetabolite, folic acid analog	
Prednisone	Receptor-mediated lympholysis plus additional mechanisms	
Anti-thymocyte globulin	Rabbit or equine antibodies against human T cells	
MMF	Inhibition of DNA synthesis → lymphocyte apoptosis	
Alemtuzumab	Humanized monoclonal antibody to CD52	
HLA-identical donor	*Matched unrelated donor*	*Unrelated cord blood*
GVHD prophylaxis combinations (pediatric studies)		
Cyclosporine for 6 months, consider low-dose 1 mg/kg/day i.v.[17,20]	Cyclosporine/methotrexate[8,19]	Cyclosporine/prednisone[9,12]
	FK506/methotrexate[19]	Cyclosporine/methotrexate/ATG[11]
	Cyclosporine/methotrexate/ATG[9]	FK506/MMF[21]
Cyclosporine/methotrexate[11,17]	FK506/methotrexate/alemtuzumab[22]	
	Therapy	*Mechanism of action*
Treatment (pediatric studies or studies that included children; refer to text for results)		
Frontline therapy	Methylprednisolone 2 mg/kg/day[36]	Receptor-mediated lympholysis plus additional mechanisms
Salvage therapy	Anti-thymocyte globulin, varying doses[25]	Rabbit or equine antibodies against human T cells
	Pentostatin 1.5 mg/m^2 × 3 days[26]	Adenosine deaminase inhibitor
	Extracorporeal photopheresis, usually 2 days/row weekly then tapering[31,37]	*Ex vivo* apoptosis of donor lymphocytes by UVA irradiation
	Daclizumab 2 mg/kg/week[27]	Humanized monoclonal IL-2 receptor antagonist
	Infliximab 10 mg/kg/week[29]	Humanized monoclonal TNF-α antibody
	Mesenchymal stem cells[33]	Immunosuppressive cells from unrelated donor that can be given across MHC barriers

Abbreviations: ATG = anti-thymocyte globulin; GVHD = graft-versus-host disease; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplantation; IL-2 = interleukin-2; i.v. = intravenous; MHC = major histocompatibility; MMF = mycophenolate mofetil; TNF-α = tumor necrosis factor-α; UVA = ultraviolet A.

outcome. It is encouraging that of the five children who were enrolled in this trial, four had a complete response.

Monoclonal antibodies have been used to treat GVHD. Daclizumab is a humanized interleukin-2 receptor antagonist that has shown some efficacy in adult studies. The Children's Hospital of Philadelphia reviewed their experience using this drug in 11 children with acute GVHD, 10 refractory to corticosteroids. Most (10) of these patients only had skin manifestations, and seven of them had an objective response. More importantly, five of these 10 children were alive at time of publication.[27] Even though this is a small, retrospective series, the data are encouraging. One has to keep in mind, though, that in a recent randomized adult study for *de novo* acute GVHD, there was more mortality from relapse and infection in patients where daclizumab was added to standard therapy.[28]

Infliximab is a monoclonal antibody that targets TNF-α. While most of the literature has been on adults, there was a recent compilation of the pediatric experience using this drug for pediatric patients with steroid-refractory GVHD. Dosing was 10 mg/kg weekly. Of 16 evaluable patients with acute GVHD, 81% had a response, with response being the greatest in the skin and GI tract. Recurrences were typical after steroid taper and/or infliximab discontinuation, as only two patients were able to maintain long-term responses.[29] As with other agents, infection remained to be a significant cause of mortality. Although retrospective, these data suggest that infliximab may have a role in controlling GVHD, but the high rate of GVHD relapse suggests that this type of therapy may not be sufficiently targeting the cause of GVHD, rather simply one of its mediators.

Another technique under investigation for treatment of acute GVHD is ECP, which is approved for cutaneous T-cell lymphoma. Briefly, leukocytes are incubated with 8-methoxypsoralen *ex vivo*, irradiated with UVA light and then returned back to the patient. Potential mechanisms of ECP-induced immune tolerance include decreased stimulation or depletion of effector T cells, increased production of anti-inflammatory or decreased production of proinflammatory cytokines and generation of T-regulatory cells. Centers have reported about a 60% response rate in patients with acute GVHD, with activity reported in liver and GI as well as skin GVHD. It appears that beginning ECP earlier in the course of GVHD may improve outcome.[30] While different treatment schedules have not been compared, most centers start with two consecutive treatments either weekly or every other week and taper based on response. Similar schedules and response rates have been reported in children.[31] Given the fluid shifts involved with ECP and the impact this may have in children, some centers have devised alternate approaches. One of them is to collect mononuclear cells using a continuous-flow separator, treat the cells *ex-vivo* with 8-methoxypsoralen and then transfer the primed lymphocyte preparation to a UVA-permeable bag and put through a UVA irradiator. Another approach is to put the mononuclear cell suspension in the UVAR XTS machine for processing (both two-step procedures).[32] Our group has been able to use the standard procedure with the UVAR

XTS in children down to 20 kg. We follow an algorithm demanding a specific hematocrit before ECP, depending on the child's weight, and normal saline is given pre-ECP depending on expected extracorporeal volume.

Finally, cellular therapy may eventually play a role in the management of GVHD. Mesenchymal stem cells (MSC) are derived from bone marrow and can differentiate into several mesenchymal tissues under proper conditions. They are not immunostimulatory *in vitro*, appear to be immunosuppressive and potentially aid in tissue repair, and can be transplanted across major histocompatibility complex barriers. The largest experience has been in Europe, and was updated at ASH 2006.[33] Forty patients with refractory acute GVHD were given MSC infusions. Nineteen received one infusion and the rest received two or more. There were 19 complete responses. A number of the patients in this report were children. Follow-up is too short to determine long-term efficacy, but this approach is promising given the immunomodulatory and tissue repairing effects of these cells.

The other issue for patients with GVHD is appropriate management of symptoms. For example, patients with severe GI GVHD and diarrhea need careful attention to fluid status, electrolyte management and protein-losing enteropathy. This is especially important in small children. There is variability among centers as for restricting oral intake during periods of active GI GVHD. Regardless, it is well known that there is significant malabsorption with GI GVHD, so children that are fed may also need supplemental parenteral nutrition. Patients with skin GVHD need to be thoroughly examined for the presence of any open sores or bullae, which may become infected. Since infectious complications are so prevalent in these patients, frequent monitoring of CMV PCR or antigenemia and appropriate therapy is important. Published Centers for Disease Control (CDC) guidelines for prevention of infection (*Pneumcystis jirovecii* pneumonia, bacterial, fungal, viral) should be closely followed.

Outcome

Unfortunately there are no definitive studies of outcome once GVHD has occurred in children. Most of these large studies have been performed in adults. The most important predictor of long-term outcome is response to primary therapy. Patients with a complete response to therapy of their GVHD have about a 50% 5-year survival as opposed to about a 30% 5-year survival in those with no or incomplete response. That study did include children and concluded that age (above or below 18 years) did not affect initial response rate to corticosteroids.[34] However more studies are needed to specifically address outcome in children with different grades of GVHD. The University of Minnesota recently published the response observed in all their patients with acute GVHD, treated uniformly. Of the 443 patients (all treated with prednisone), durable responses were obtained in 245 (55%). There was a tendency to a lower response if patients begun with a higher grade. Recipients of HLA-mismatched unrelated donor transplants were less likely to respond. Fifty-three percent of patients were alive at 1 year after initiation of steroid therapy, and 42% of patients had developed chronic GVHD. Deaths were mostly commonly attributed to ongoing GVHD and/or infection.[35] When looking at patients by grade, those with grade III acute GVHD have about a 30% probability of long-term survival. Those with grade intravenous acute GVHD have less than 5% long-term survival.[5]

Conclusions

The last decade has brought exciting changes to the pediatric HSCT picture. We are moving transplantation to the forefront of treatment for certain non-malignant diseases. We are demonstrating similar results in many cases using alternative donor stem cell sources as compared with matched-sibling donor transplants. To capitalize on these recent gains and since GVHD continues to be a barrier to successful HSCT, we must strive as a pediatric community to come together and perform well-organized clinical trials that address both prophylaxis and salvage treatment of acute GVHD in children.

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