Bone Marrow Transplantation (2008) 42, S101–S105

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REVIEW

Innovative approaches to treat steroid-resistant or steroid refractory GVHD

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First-line treatment of GVHD is based on steroids and produces sustained responses in 50–80% of patients with acute GVHD (aGVHD) and 40–50% of patients with chronic GVHD (cGVHD) depending on the initial disease severity. Non-responding children are offered second-line therapy with combinations of various agents, but currently available agents have not improved survival in these high-risk populations. In this minireview, we will focus on new agents to treat GVHD in paediatric patients.
Bone Marrow Transplantation (2008) **42,** S101–S105; doi:10.1038/bmt.2008.294
Keywords: GVHD; new approaches; steroids

Introduction

GVHD is the most frequent complication after allogeneic haematopoietic HSCT. First described as a 'secondary disease' in mice,[1] the syndrome was shown to be triggered by immunocompetent donor cells.[2,3] As soon as the clinical basis for human HSCT was established, it was apparent that GVHD would be an important problem even with the transplantation of marrow cells from sibling donors. Despite improvements in post-transplant immunosuppression, up to 30% of HLA-identical marrow graft recipients and up to 90% of patients receiving marrow from unrelated donors still develop significant acute GVHD (aGVHD).[1–3] Prednisone has been shown to be effective in the treatment of established aGVHD.[4] However, patients not responding to corticosteroids at day 5 are at high risk of death, with a TRM of 46% as compared with 16% for good responders.[5,6] Despite aggressive treatment, chronic GVHD (cGVHD) affects 50% of long-term marrow transplant survivors and is lethal in 20–40% of affected patients.[1,7] Primary therapy for extensive cGVHD usually includes corticosteroids and CsA.[8,9] Previously published studies documented a lower risk of aGVHD and cGVHD in younger patients, but only a few studies focused specially on children.[10–16] New treatments are now available for steroid-resistant or refractory GVHD and these will be reported in this paper.

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Steroid-resistant or refractory aGVHD

Historically, patients with severe aGVHD graded III–IV were treated with higher doses of steroids ± serotherapy, but results were mainly not reproducible. Experimental studies have proposed new drugs in the treatment of GVHD, although very few were randomized multicentre studies.

Anti-IL-2 receptor Abs

Abs, polyclonal or monoclonal, are the most widely used secondary agents. There is considerable experience with antithymocyte globulin, which has been in use for more than three decades. A broad array of MoAbs in murine or humanized form with pan-T or T-subset reactivity has been used as secondary therapy of GVHD. Responses, sometimes sustained, have been observed.

(1) *Daclizumab*: It is a humanized monoclonal IgG1, which binds the α-chain of IL-2 receptor. Lee *et al.* administered methylprednisolone in association with daclizumab 1 mg/kg or placebo on study days 1, 4, 8 and weekly as long as clinically indicated. The groups ($N = 53$, median age 45 years (18–59) and 42 years (8–65), respectively) were balanced for clinical characteristics. GVHD response rates by study day 42 were similar (53 vs 51%; $P = 0.85$). The study was halted after a planned interim analysis and showed a significantly worse 100-day survival in the group receiving corticosteroids plus daclizumab (77 vs 94%; $P = 0.02$). Overall survival at 1 year was also lower in the combination group arm (29 vs 60%; $P = 0.002$). Both relapse- and GVHD-related mortality contributed to the increased mortality in the combination group.[17] Recently, Bordigoni *et al.* administered daclizumab as a single second-line agent to treat 62 patients (median age 25 years (1.5–53)). The overall response rate was 69% and 4-year EFS was 54.6%, showing that daclizumab is a suitable alternative for the treatment of aGVHD

when limited to the skin or to the gastrointestinal tract.[18]

(2) *Denileukin*: Denileukin diftitox (Ontak) is a recombinant protein composed of human IL-2 fused to diphtheria toxin. It has selective cytotoxicity against activated lymphocytes expressing the high-affinity IL-2 receptor. A phase 1 study of denileukin diftitox in 30 patients (median age 43 years (20–63)) with steroid refractory aGVHD showed that 71% of patients responded with a complete resolution (12 of 24; 50%) or a partial resolution (5 of 24; 21%) of aGVHD. Eight out of 24 patients (33%) are alive at 6.3–24.6 months (median 7.2).[19]

(3) *Inolimomab*: Inolimomab is a murine anti-IL-2R. Eighty-five patients (median age 29 years (2 months–61 years)) were evaluated retrospectively for the safety and efficacy of inolimomab given for the treatment of steroid-resistant aGVHD. Inolimomab was administered in the event of steroid-resistant aGVHD with a median dose of 0.468 mg/kg (median duration of treatment: 18 days). Twenty-five complete responses (CRs) and 29 partial responses (total response rate: 63%) were observed with no side effects, although better responses were observed in skin aGVHD. Inolimomab is well tolerated and effective for severe steroid-resistant aGVHD.[20]

(4) *Basiliximab*: Basiliximab is a chimeric MoAb that binds to the α-chain of IL-2R on activated cytotoxic T cells, inhibiting their proliferation. Thirty-four patients (median age 13 years) were evaluated. CRs were seen in 27 of 32 patients (84%) with skin, 12 of 25 (48%) with gut and 6 of 23 (26%) with liver aGVHD. The median duration of response was 38 days (5–1103). In conclusion, basiliximab induced CRs in patients with refractory aGVHD. Prospective studies are necessary to evaluate the optimal treatment schedule.[21]

Anti-CD3 Ab

Humanized non-FcR-binding anti-CD3 MoAb visilizumab was given to 44 patients (median age 43 years (3–69)) at a single dose of 3 mg/m^2 with complete response (CR) and overall response rates of 14 and 32%, respectively. Further assessment on its use needs to be made.[22]

Anti-T cell–APC interaction

The ligation of CD2, expressed on T and NK cells, with the LFA-3 (CD58) Ag on the APC provides a stable platform for TCR–HLA interactions, as well as serving a co-stimulatory function with a critical function in allo-Ag reactivity. Alefacept combines the first extracellular domain of LFA-3 with the Fc portion of IgG1, and binds CD2 on the surface of T cells, blocking T cell–APC interactions as well as triggering apoptosis of T cells through its interaction with FCcRIII on effector cells. Three adult patients (median age 54 years (38–57)) were treated with Alefacept. One patient with aGVHD and two with extensive cGVHD benefited from Alefacept administration given as an outpatient regimen, and it is now being tested in a phase I/II study of steroid-resistant GVHD.[23]

Anti-CD147 Abs

ABX-CBL, an IgM murine MoAb, recognizes CD147 and initiates cell killing through complement-mediated lysis. CD147 is expressed weakly on human leukocytes, granulocytes, RBC and several other cell types. On activation, CD147 is upregulated on T and B lymphocytes. Activated T cells (CD4$^+$ and CD8$^+$) and B cells, as well as resting and activated monocytes and DC, are depleted by ABX-CBL *in vitro*, whereas resting lymphocytes remain unaffected. ABX-CBL inhibits the *in vitro* MLR by depleting monocytes, DC and activated lymphocytes through a complement-dependent cytotoxic mechanism. Among 51 patients (median age 36 years (1–59)) who could be evaluated for efficacy, 26 (51%) responded, including 13 with CR and 13 with partial responses. Twenty-six (44%) patients were still alive 6 months after initiating ABX-CBL therapy. These results are encouraging, but further studies on the use of ABX-CBL in the management of GVHD are warranted.[24]

Anti-TNF Abs

Tumour necrosis factor-α (TNF-α) is an important cytokine involved in the development of GVHD, and earlier studies have shown the possible benefit of anti-TNF-α Ab administration in treating GVHD. Abs to TNF (infliximab) or to the TNF receptor (etanercept) have been developed and also used in the second-line treatment of aGVHD.[25–27] Responses have been observed with some patients clearing their symptoms rapidly. Infections, however, remain an issue.

Immunoregulatory cell therapy

(1) *MSCs*: Multipotent MSCs have immunomodulatory effects. Patients with post-transplant complications based on deregulated immune effector cells may benefit from an immunomodulatory effect of MSCs by its homostatic role of T-cell subsets. MSCs reduce the secretion of IFN-γ by IL-2-stimulated NK cells, but do not inhibit their K562 lysis.[28] Several factors have been suggested to induce T-cell suppression by MSCs *in vitro*, including among those hepatocyte growth factor and transforming growth factor-β1, IL-2, indoleamine 2,3-dioxygenase, prostaglandin E2, and IL-10.[29–33] MSCs are generally given in escalating doses by i.v. transfusion. No severe reactions have been documented even when third-party MSCs were transplanted.[34,35] Ning *et al*. recently reported a 60% relapse rate vs a 20% relapse rate in patients treated with a co-infusion of MSCs and HSCs to prevent GVHD. These data need to be considered in the evaluation of new protocols for the treatment of GVHD.[36]

(2) Extracorporeal photopheresis (ECP) has mostly been used in patients with cGVHD, and significant responses have been seen in a proportion of patients. ECP has objective activity in the treatment of aGVHD and cGVHD,[37,38] including cases of liver and lung GVHD where more objective, measurable response parameters are available. The mechanism of ECP action has not been elucidated fully. Previous reports appear to show that ECP modulates DC populations: in GVHD,

a decrease in circulating $CD80^+$ and $CD123^+$ DCs and a decrease of DC function was noted after ECP,[39] together with a shift from myeloid DCs to plasmacytoid DCs and a shift from a Th1 cytokine profile to a Th2 cytokine profile;[40] however, these findings are not generally accepted and the effects of ECP on *in vivo* DC homoeostasis still remain unclear. In a recent published paper, an *in vitro* model of ECP-treated lymphocytes with immature DC co-cultured a significantly reduced CD54, CD40 and CD86 mean fluorescence intensity after lipopolysaccharide stimulation was shown. In the same model, DCs produced increased amounts of IL-10 when co-cultured with ECP-treated lymphocytes and stimulated with lipopolysaccharide, whereas IL-12 and TNF-α production were not affected. Di Renzo *et al*.,[41] stated that reinfusion of large numbers of autologous apoptotic lymphocytes is significant for the therapeutic outcome of ECP through downregulation of co-stimulatory molecules on DCs, inducing non-fully mature DCs with a low signal 2 and upregulation of IL-10, which is an immunosuppressive cytokine. Overall, the procedure is well tolerated and no fatal toxicities have been reported so far in the literature. Our experience in children (median age 10.8 years (5.8–18)) also confirms the activity in steroid-resistant aGVHD, especially for patients having skin-limited aGVHD. Our study suggests the ECP response as a strong predictor of TRM, as non-responder patients are at higher risk and, more importantly, the prognosis of this patient group is severe, as no other therapies can rescue them.[42]

Steroid-resistant or refractory cGVHD

Steroid-refractory cGVHD is formally defined as either failure to improve after at least 2 months or progression after 1 month of standard immunosuppressive therapy, including corticosteroids and CSA.[37,38] cGVHD is associated with a GVL effect, thus resulting in a decreased probability of relapse. Nevertheless, the reduced relapse risk is offset by an increase of TRM and counterbalanced by a severely impaired quality of life for patients who experienced the extensive form of the disease.[16]

ECP

ECP has been studied extensively in cGVHD treatment. The mechanism of action of ECP has not been elucidated fully. As stated above previous reports appear to show that ECP modulates DC populations by reducing expression of co-stimulatory molecules such as CD80 and CD86,[39,41] together with a shift from myeloid DCs to plasmacytoid DCs and a shift from a Th1 cytokine to a Th2 cytokine profile.[40,41] Objective responses have been observed in a substantial number of patients with both skin and visceral cGVHD failing corticosteroids and other treatments. Our results in cGVHD paediatric patients (median age 11.9 years (7–18.5)) support previous reports of objective responses of skin and visceral GVHD to ECP.[42] Importantly, ECP procedures are also feasible for low-weight children ($\leqslant$12 kg), and a very low rate of infection complications owing to central line catheter manipulations have been observed.

Imatinib mesylate

Extensive cGVHD is characterized by fibrosis similar to that of patients with systemic sclerosis (scleroderma). As stimulatory auto-Abs against the PDGF receptor (PDGFR) have been found in patients with scleroderma and are responsible for the activation of skin fibroblasts, serum samples from 39 patients (22 with cGVHD and 17 without cGVHD) and 20 healthy controls were assayed for the presence of stimulatory auto-Abs to the PDGFR. Stimulatory Abs to the PDGFR were found selectively in all patients with cGVHD but in none of the patients without cGVHD. Higher levels were detected in patients with generalized skin involvement and/or lung fibrosis. Abs recognized native PDGFR, induced tyrosine phosphorylation and accumulation of reactive oxygen species and stimulated type 1 collagen gene expression through the Ha-Ras–ERK1/2–reactive oxygen species signalling pathway.[43] *In vitro* studies have shown that imatinib strongly inhibits the growth of cutaneous fibroblasts and that in all forms of fibrosis, fibroblasts and myofibroblasts are the most predominant cells.[44,45]

Anti-CD20 Ab

There is now mounting evidence implicating B cells in the pathophysiology of cGVHD. Abs to Y chromosome-encoded mHA are generated after sex-mismatched allogeneic transplantation, and the presence of these Abs has been correlated with the occurrence of cGVHD and a decreased risk of relapse. The finding of a coordinated Ab response in the context of cGVHD generates the hypothesis that specific anti-B-cell therapy may be effective for cGVHD. The anti-CD20 chimeric MoAb rituximab has recently been shown to induce significant clinical response in a proportion of patients with refractory cGVHD. A retrospective analysis of 38 patients (median age 48 years (22–61)) evidenced an overall response rate of 65%, with an actuarial 2-year survival of 76%.[46]

Cutler *et al*. designed a phase 1/2 study with rituximab in steroid-refractory cGVHD where 21 adult patients (median age 42 years (21–62)) were treated with 38 cycles of rituximab. The clinical response rate was 70%. Responses were limited to patients with cutaneous and musculoskeletal manifestations of cGVHD that lasted over a year after therapy.[47]

Conclusions

Steroid-resistant or refractory GVHD continues to be a major issue in the stem cell transplant era. New knowledge has improved our ability to prevent GVHD, although if GVHD develops, it can be seen that there have been no significant improvements in the last decade.

New data from the literature are intriguing and we need to bear in mind the following suggestions:

- Each patient with steroid-resistant/refractory GVHD should enter a clinical trial.

- As the aetiology of aGVHD is mainly based on T-cell alloreactivity, T-cell-directed therapy is probably beneficial for these aGVHD patients (the best anti-T-cell therapy is still unknown). MSCs are of great interest, but leukaemia recurrence remains a challenge.
- As the aetiology of cGVHD is less known, a broad spectrum of immunosuppressive agents have been tested. Ongoing research to further characterize the pathogenesis of this disease is crucial to develop new therapeutic approaches. An improved strategy should be individualized, but a multidisciplinary approach is always warranted. We suggest that (a) if skin or oral mucosae cGVHD is diagnosed, the ECP therapy needs to be considered as soon as possible. Excellent *in vitro* results have shed some light on imatinib mesylated for sclerodermic cGVHD, and ongoing randomized clinical trials are starting now in Italy. (b) When visceral organ involvement is proven, the chosen therapy should be target organ directed (for example, tacrolimus for liver cGVHD, anti-TNF-α for gut cGVHD, and steroids for lung cGVHD).

Conflict of interest

The authors have declared no financial interests.

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