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Therapy of acute graft-versus-host disease

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Abstract

Primary therapy of acute GvHD grade II–IV is still based on the systemic application of corticosteroids at doses of 1–2 mg/kg (e.g. prednisolone). Typically, investigators combine this approach with therapeutic doses of calcineurin inhibitors, which are used as prophylactic regimens. Patients not responding to steroids within 5–7 days or those with progressive disease within 72 hours represent a high-risk population that requires further immunosuppressive escalation. Pharmacological second-line therapy is mainly based on centre policies and individual decisions since no strategy has been associated with an improvement in survival within a controlled prospective trial. Compounds with efficacy in phase II trials are mycophenolate mofetil, methotrexate, pentostatin, mTOR inhibitors, antibodies targeting TNF-alpha or IL-2 pathways, and monoclonal or polyclonal anti-T cell antibodies. Non-pharmacological options include extracorporeal photopheresis and the infusion of allogeneic mesenchymal stromal cells. For most interventions, earlier treatment (e.g., within two weeks) is associated with a better outcome. However, the overall efficacy and toxicity of most approaches are unsatisfactory. Future developments include the use of regulatory T cells and more targeted approaches using small molecules interacting with specific signalling pathways of antigen-presenting and effector cells.

Keywords: acute graft-versus-host disease, refractory, salvage therapy, toxicity, tolerance

Introduction

Acute graft-versus-host disease (aGvHD) is one of the major complications following allogeneic hematopoietic stem cell transplantation (aHSCT). The success of aHSCT relies on how well transplant-related morbidity and mortality can be controlled while preserving the graft-versus-leukemia (GvL) effect essential to prevent relapse. It is important to understand the underlying mechanisms and effectors of aGvHD in order to prevent this complication.

According to Billingham‘s Harvey lecture in 1966 there are three requirements for aGvHD to develop. “First, the graft must contain a sufficient number of immunologically competent cells. Second, the host must possess important transplantation alloantigens that are lacking in the donor graft, so that the host appears foreign to the graft, and is, therefore, capable of stimulating it in an antigen dependent manner. Third, the host itself must be incapable of mounting an effective immunological reaction against the graft, at least for sufficient time for the latter to manifest its immunological capabilities; that is, it must have the security to tenure.” for review see [9].

The incidence of aGvHD ranges from 40% to 80% and depends on known risk factors like age, donor relationship, HLA-match, sex, graft source, and type of immunosuppressive prophylaxis. The mortality associated with acute GvHD can be directly correlated with the clinical grade at the time of manifestation and the initial response to steroid therapy [6,28]. In addition, the time of occurrence and the grading at given time-points after transplantation seems to be relevant for the prognosis of an individual patient [19].

Primary therapy

The three organs most affected by aGvHD are the skin, gastrointestinal tract, and liver. Typically, either > grade 1 skin involvement or visceral manifestations are observed before therapy is institut-

ed. The restrictive use of steroids is mainly due to the morbidity and complications associated with high dose steroid therapy in patients who have undergone serial chemotherapy and conditioning therapy. An alternative approach would be to use lower doses of steroids earlier in the course of the disease.

In a recent retrospective analysis, Mielcarek and coworkers compared the outcome of patients with acute GvHD grade I–IV receiving either 1 or 2 mg/kg prednisolone [22]. The cumulative dose of steroids applied in the latter group was significantly higher compared to patients starting at lower doses, and this was associated with a higher incidence of invasive fungal infections and a prolonged hospital stay. The authors conclude that patients with grade I–II acute GvHD may only require 1 mg/kg prednisolone and do not benefit from higher doses. Most investigators try to achieve higher trough-blood levels of the concomitantly applied calcineurin inhibitors (e.g., Cyclosporine or Tacrolimus), which in most cases of acute GvHD are still part of the patients' medication.

Salvage therapy

Definition

In most clinical trials steroid-refractory acute GvHD is defined as no improvement of symptoms after 5–7 days or progressive disease within 72 hours after the start of therapy.

These patients should receive second line therapy, ideally within a clinical trial. As there are not many pharmaceutical companies which are willing to sponsor clinical studies and academic institutions are paralyzed by current legislation, the majority of patients can not be included in such trials. Therefore the current table provides a number of compounds tested in prospective phase I/II trials with the respective response rates observed. Only very few prospective controlled clinical protocols have been performed for this indication and have not been able to demonstrate an advantage in overall survival.

Agent	N	Response rate	Citation
Antithymocyte globulin	47	54%	(MacMillan et al., 2002)
Mycophenolate mofetil	17	65%	(Basara et al., 1998)
Pentostatin	23	74%	(Bolanos-Meade et al., 2005)
Etanercept	13	46%	(Busca et al., 2007)
Denileukin difitox	30	71%	(Ho et al., 2004)
Basiliximab	23	83%	(Schmidt-Hieber et al., 2005)
Daclizumab	43	51%	(Przepiorka et al., 2000)
Infliximab	32	59%	(Patriarca et al., 2004)
Visilizumab	44	32%	(Carpenter et al., 2005)
Orthoclone	43	69%	(Knop et al., 2005)
MabCampath	16	50%	(Gomez-Almaguer et al., 2008)
Sirolimus	21	55%	(Benito et al., 2001)

Prospective controlled trials

Only very few of the aforementioned agents have been tested in randomized controlled trials. In first line therapy, daclizumab, an antibody competitively blocking the IL-2 receptor, when combined with steroids was prospectively compared with steroids alone [18]. Despite the encouraging phase II trials in steroid refractory disease, the combined use of this anti-CD25 antibody and steroids was associated with an inferior survival compared to the control arm. Similarly, anti-CD147 therapy compared with antithymocyte globulin (ATG) has lead to a non-significant survival disadvantage [20]. An European trial investigating the use of a murine anti-CD3 antibody (Orthoclone) for which production will be discontinued in 2010 has suggested a non-significant advantage for the combination of high-dose steroids (HDS) combined with orthoclone compared to HDS alone [15]. The lack of support by pharmaceutical companies and the difficulties with trial design and end-points in steroid refractory GvHD have currently abrogated most efforts in this area of clinical research.

Current strategies inaugurated by multi-institutional trial networks include randomized phase II trials with several arms which are designed to identify differences in survival early with the aim of switching to a phase III part of the trial thereafter. One recent example is the study published by Alousi et al which suggests an advantage for the combination of MMF with steroids [1]. Further follow-up is needed to confirm these findings.

Non-pharmacological interventions

Extracorporeal photopheresis

Very exciting results have been recently published for the effectiveness of extracorporeal photopheresis (ECP) by Greinix and coworkers. They have clearly demonstrated that interesting response rates can be achieved by the early use of ECP with minimal toxicity and the possibility of reduce steroid therapy earlier [12]. Current efforts have to confirm this single-institution experience in a prospective multicentre trial.

Mesenchymal stromal cells (MSC)

MSC were described two decades ago by Friedenstein [10]. Since that time their potential for regenerative therapies has been the focus of many research groups. In the recent past, their immunosuppressive and anti-inflammatory activity has been addressed and confirmed in-vitro and in-vivo. Katarina Le Blanc and coworkers described the first successful therapeutic use of donor-derived MSC in steroid-refractory GvHD [16]. Since then, several investigators have confirmed the potential use of MSC in patients with advanced GvHD [17]. The different cellular preparations and application protocols so far do not allow firm conclusions on the efficacy of MSC therapy in various settings to be drawn. Prospective randomized trials are currently under-way and will shed more light on this cellular therapeutic approach. One advantage over most alternative pharmacological strategies is that MSC infusion is not associated with acute and mid-term side effects of an increased rate of infectious complications.

Regulator T cells (Tregs)

Since the pivotal studies of Edinger and coworkers demonstrating the efficacy of the prophylactic infusion of donor-derived CD4+/CD25++/Foxp3+ regulatory T cells in a murine models [8], several translational research activities have tried to prepare the first human trials using donor or patient-derived regulatory T cells. Most intriguing are the findings of the preclinical studies in which the anti-leukemic efficacy of adoptively transferred donor effector cells (GvL reactions) were not suppressed by the co-infusion of Tregs. The current challenge is to develop clinical-grade strategies to generate a sufficient amount of pure Tregs for repetitive infusions. In-vitro selection and expansion protocols have been described and need further refinement to avoid the application of activated CD25+ T cells. Recent case reports and preliminary clinical data suggest that beside their prophylactic use, the therapeutic efficacy of Tregs may be expected in certain clinical situations [23]. Current clinical protocols have additionally focussed on the use of donor Tregs to allow infusion of conventional T cells ameliorating immune reconstitution in the haploidentical setting without the induction of GvHD. Dose-finding and feasibility studies are needed in order to develop Tregs into an additionalas therapeutic tool in high-risk patients with acute GvHD.

Supportive care

Many of the intensified immunosuppressive regimens described above leave the patient at an increased risk for opportunistic infections. Beside the use of pre-emptive antiviral therapy to control CMV reactivation occurring during the course of refractory GvHD, invasive fungal infections are the major threat for patients with GvHD undergoing intensified and prolonged immunosuppressive therapy. The development of new antifungal agents have definitively helped to ameliorate the perspectives for patients with acute GvHD. Current recommendations favour the use of prophylactic antifungal medication in patients receiving > 1–2 mg of systemic steroids. A prospective randomized trial of posaconazole vs. fluconazole suggested that compounds effective against aspergillus species are especially warranted in this indication [27].

Perspectives

Since the outcome of patients with acute GvHD not responding to primary therapy with steroids still remains unsatisfactory, future strategies will have to focus on the following questions.

• How can we predict the individual risk for the occurrence of GVHD and the chance for responding to steroids by using genetic screening methods besides the standard high-resolution HLA typing methods (e.g., Cytokine gene polymorphisms)?

• What is the optimum pharmacological or cellular therapy approach for each patient?

• Which strategies can be applied with synergy?

• Can new molecularly-defined approaches using small molecules that specifically target signalling pathways involved in the pathophysiology be implemented with less off-target toxicities?

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