Graft-*versus*-host disease therapy: something else beyond glucocorticoids?

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Graft-*versus*-host disease (GVHD) remains the main complication and limitation to successful allogeneic hematopoietic stem cell transplantation (alloSCT). Although a decreased incidence of severe GVHD has been reported throughout the last 20 years, acute and chronic GVHD events still have a great impact on early and late non-relapsed mortality and on the quality of life of long-term survivors.[1] In spite of significant advances in the understanding of the pathophysiology of GVHD and the development of more targeted immunosuppressive therapies, glucocorticoids remain the gold standard for therapy for acute and chronic GVHD. However, the results of glucocorticoid treatment are clearly suboptimal, with continuing complete response rates of only 20-40% in acute and chronic GVHD.[2-3] Moreover, the administration of high doses and/or prolonged use of glucocorticoids is associated with severe side effects, such as opportunistic infections, diabetes, myopathy, and osteonecrosis, that are significant factors for morbidity and mortality. It still remains a matter of debate whether there is an alternative therapy to glucocorticoids that can overcome these problems. In this issue of Haematologica, Pidala *et al*. report results of sirolimus as an alternative to glucocorticoids in the first-line treatment of acute GVHD.[4] In a second article, van Dorp *et al*. evaluate the changes in lymphocyte subsets before and after rituximab treatment in responding and non-responding patients with steroid-refractory chronic GVHD.[5]

Glucocorticoids are the most effective anti-inflammatory drugs available for the treatment of many inflammatory and immune diseases. Their main action is in switching off multiple activated inflammatory genes that encode for cytokines such as IL-2, TNF-α, chemokines, adhesion molecules, inflammatory enzymes and receptors.[6] In addition, glucocorticoids increase transcription of several anti-inflammatory or inhibitory cytokine genes such as IL-10, IL-12 or IL-1 receptor antagonists.[6] Most of these cytokines have been involved in the pathophysiology of GVHD.

Pathophysiology of graft-versus-host disease

The classical scheme of the development of acute GVDH includes three main distinct yet inter-related phases.[7] The first phase is initiated by the release of proinflammatory cytokines (IL-1, IL-8, TNF-α) from host tissues that have been damaged by the transplant conditioning regime, underlying diseases and prior infections. There is a subsequent activation and maturation of antigen-presenting cells and donor T cells. In a second phase, the activation of the immune cells results in transcription of genes for many proteins including cytokines, mainly Th1 cytokines (IFN-γ, IL-2 and TNF-α), and their receptors. In the final phase, T cells migrate to GVHD target tissues (skin, gut, liver, and lungs) and recruit other effector cells, such as cytotoxic T lymphocytes and NK cells, leading to host tissue damage.

Relatively little is known about the pathophysiology of chronic GVHD in comparison to acute GVHD. Several mechanisms have been involved in its pathogenesis such as a persistence of donor-derived alloreactive T cells, a Th1-Th2 shift of the cellular immune response, autoreactive T cells arising from control failure by regulatory T cells and/or impaired negative selection of T cells in the thymus, an increasing role of B cells producing auto- and allo-antibodies against the host, and unspecific mechanisms of chronic inflammation leading to fibrosis in the organs involved.[8-10]

First-line treatment of acute graft-versus-host disease

In order to increase the response rate of the initial treatment of acute GVHD and/or reduce glucocorticoid exposure, several studies have tested the efficacy of adding another immunosuppressant agent to glucocorticoids.

In a controlled clinical trial, patients were randomized to be treated with prednisone *versus* antithymocyte globuline (ATG) plus prednisone.[11] An intent-to-treat analysis of the overall response at day 42 showed equivalent complete partial response rates of 76% in both the prednisone and ATG/prednisone therapy groups. However, patients in the ATG/prednisone arm experienced more infections with cytomegalovirus and more frequent pneumonitis. There was no significant difference in survival at two years between the two treatment arms. As previously shown, one of the most important inflammatory cytokines involved in the process of acute GVHD is TNFα. Based on that, etanercept, an anti-TNFα agent, has been added to prednisone and tested as initial therapy for acute GVHD in a phase II clinical trial.[12] The outcome of these patients was compared with those of patients with GVHD undergoing therapy at the same time whose initial treatment was prednisone alone. Patients treated with etanercept were more likely to achieve complete remission at four weeks than patients treated with steroids alone (69% *vs.* 33%). Moreover, the addition of etanercept resulted in a higher response rate in all target organs, skin, gastrointestinal tract and liver. Another promising combination for initial therapy of acute GVHD consists of glucocorticoids and mycophenolate mofetil (MMF). In a randomized, 4-arm, phase II trial, 180 patients received methylprednisolone plus either etanercept, MMF, denileukin diftitox, or pentostatine. Methylprednisolone plus MMF resulted in the highest 28-day complete response rate.[13] In addition, MMF offered the greatest probability of survival and the lowest cumulative incidence of severe infections.

Only a few agents have been tested as alternatives to glucocorticoids for first-line treatment of acute GVHD. These studies were performed in the 1980s and with only a few patients. In a prospective trial, 37 patients were randomized to receive ATG *versus* glucocorticoids.[14] There was no difference between treatment groups in GVHD response rate, incidence of infectious complications, or survival. In another study, 48 patients who had received methotrexate as GVHD prophylaxis and developed acute GVHD II-IV were treated with a combination of ATG and cyclosporine, with or without the addition of methylprednisolone.[15] No benefit was observed in those patients treated with methylprednisolone in terms of GVHD response, infections or survival.

In this issue of Haematologica, Pidala *et al.* show that initial treatment of acute GVHD with sirolimus results in a comparable response rate to that of high-dose glucocorticoids.[4] Sirolimus (rapamycin) is a macrocyclic triene antibiotic with immunosuppressive, antitumor and antifungal properties. Sirolimus prevents T- and B-cell activation by cytokines, which in turn prevents cell cycle progression and proliferation. Sirolimus has been reported to be active in combination with tacrolimus for GVHD prophylaxis, and in the treatment of steroid-refractory acute and chronic GVHD.[16-18] A glucocorticoid-free first-line treatment of acute GVHD with sirolimus is an attractive approach. However, despite encouraging results showed by Pidala *et al*., the low number of patients included in the study, particularly those with over grade II acute GVHD, makes it difficult to come to any conclusions as to a hypothetical superiority of sirolimus against glucocorticoids. Prospective controlled trials are warranted to assess the impact of sirolimus on response rate in acute GVHD and on overall survival.

Treatment of chronic graft-versus-host disease

Distinction between classical chronic GVHD, overlap syndrome, and late acute GVHD as described by the National Institutes of Health (NIH) consensus criteria is mandatory to establish treatment strategy of chronic GVHD.[19] Thus, late acute GVHD and overlap syndrome with dominating acute features should be treated according to standard practice in the treatment of acute GVHD. The treatment should also be guided by the presence of risk factors such as low numbers of platelets at diagnosis, extensive skin disease (>50% of body surface) and severe chronic GVHD (NIH grading). Decision making concerning the type of treatment for chronic GVHD should also take into consideration the risk of relapse if the patient undergoes transplant for a hematologic malignancy, including the risk of severe infections, and other secondary effects such as diabetes, nephrotoxicity, or arterial hypertension.

The use of glucocorticoids is the standard of care for chronic GVHD.[20] Although controversial, upfront use of the combination of prednisone and a calcineurin inhibitor may be useful in patients with high risk of mortality and/or high risk for steroid toxicity. Half of the patients fail to achieve a long-lasting response to first-line treatment. Unfortunately, additional systemic immunosuppressive agents, such as thalidomide, MMF, and azathioprine, have failed to improve treatment results in the primary treatment of chronic GVHD and are in part associated with higher morbidity, and in the case of azathioprine, with higher mortality. In the setting of steroid-refractory chronic GVHD, a large number of drugs and other immunomodulatory treatments have been used with variable results.[21] One of these drugs is rituximab which has a growing role in the prevention and treatment of GVHD. It has been used with relative success in the treatment of steroid-refractory chronic GVHD, particularly in cases where skin and mucosal are involved. In a systematic review and meta-analysis of seven studies with a total of 111 patients, the organ-specific response rate was extremely variable, and the pooled proportion of overall response rate was 66% (95% CI 57-74%).[22] Some of these studies suggest that rituximab facilitates a reduction of glucocorticoid dosage, mostly in cases of steroid-refractory chronic GVHD involving the skin and oral mucosa.

Since the response of chronic GVHD is often uncertain, and mixed responses in different organs can occur in the same patient, it would be interesting to investigate which factors can predict response to treatment. In this issue of Haematologica, van Dorp *et al.* evaluate clinical efficacy and changes in lymphocyte subsets before and after rituximab treatment in a prospective phase II study in 20 patients with steroid-refractory chronic GVHD.[5] The overall response rate was 61%. Interestingly, an elevation of B-cell numbers with a dominant naïve, antigen-presenting phenotype, as well as skewing towards CD5- B cells and B cells with a low CD5 expression, was selectively found in responding patients and was the only predictive factor of rituximab responsiveness.

Novel perspectives

After a long period of time with no significant developments in the setting of prophylaxis and first-line treatment of GVHD, the search for novel approaches to GVHD has accelerated. Substantial progress has been made in the identification of biomarkers for GVHD with diagnostic and prognostic significance. IL-2-receptor-α, TNF-receptor-1, IL-8, hepatocyte growth factor, elafine, REG3-α, and regulatory T cells have been recently described as biomarkers for diagnosis of acute GVHD that also predict response to first-line treatment and survival.[23] These findings may lead to the development of innovative strategies such as the preemptive treatment of GVHD. A risk stratification of GVHD that combines both biomarkers and clinical grade could ultimately guide the intensity and duration of GVHD treatment to minimize the toxicities related to glucocorticoid administration. The use of biomarkers as predictors of GVHD response combined with the development of glucocorticoid-free first-line treatment strategies, as shown by van Dorp *et al*. and Pidala *et al*. in this issue of Haematologica, are also promising approaches in the management of GVHD.

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References

1. Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med. 2010;363(22):2091-101.
2. Martin PJ, Schoch G, Fisher L, Byers V, Anasetti C, Appelbaum FR, et al. A retrospective analysis of therapy for acute graft-versus host disease: initial treatment. Blood. 1990;76(8):1464-72.
3. Vogelsang GB. How I treat chronic graft-versus-host disease. Blood. 2001;97(5):1196-201.
4. Pidala J, Tomblyn M, Nishihori T, Field T, Ayala E, Perkins J, et al. Sirolimus demonstrates activity in the primary therapy of acute graft-versus-host disease without systemic glucocorticoids. Haematologica. 2011;96(9):1351-6.
5. van Dorp S, Resemann H, te Boome L, Pietersma F, van Baarle D, Gmelig-Meyling F, et al. The immunological phenotype of rituximab-sensitive chronic graft-versus-host disease: a phase II study. Haematologica. 2011;96(9):1380-4.
6. Zen M, Canova M, Campana C, Bettio S, Nalotto L, Rampudda M, et al. The kaleidoscope of glucocorticoid effects on immune system. Autoimmun Rev. 2011;10(6):305-10.
7. Socié G, Blazar BR. Acute graft-versus-host disease: from the bench to the bedside. Blood. 2009;114(20):4327-36.
8. Tivol E, Komorowski R, Drobyski WR. Emergent autoimmunity in graft-versus-host disease. Blood. 2005;105(12):4885-91.
9. Miklos DB, Kim HT, Miller KH, Guo L, Zorn E, Lee SJ, et al. Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. Blood. 2005; 105(7):2973-8.
10. Sarantopoulos S, Stevenson KE, Kim HT, Cutler CS, Bhuiya NS, Schowalter M, et al. Altered B-cell homeostasis and excess BAFF in human chronic graft-versus-host disease. Blood. 2009;113(6):3865-74.
11. Cragg L, Blazar BR, Defor T, Kolatker N, Miller W, Kersey J, et al. A randomized trial comparing prednisone with antithymocyte globulin/prednisone as an initial systemic therapy for moderately severe acute graft-versus-host disease. Biol Blood Marrow Transplant. 2000; 6(4A):441-7.
12. Levine JE, Paczesny S, Mineishi S, Braun T, Choi SW, Hutchinson RJ, et al. Etanercept plus methylprednisolone as initial therapy for acute graft-versus-host disease. Blood. 2008;111(4):2470-5.
13. Alousi AM, Weisdorf DJ, Logan BR, Bolaños-Meade J, Carter S, Difronzo N, et al. Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. Blood. 2009;114(3):511-7.
14. Doney KC, Weiden PL, Storb R, Thomas ED. Treatment of graft-versus-host disease in human allogeneic marrow graft recipients: a randomized trial comparing antithymocyte globulin and corticosteroids. Am J Hematol. 1981;11(1):1-8.
15. Deeg HJ, Loughran TP Jr, Storb R, Kennedy MS, Sullivan KM, Doney K, et al. Treatment of human acute graft-versus-host disease with antithymocyte globulin and cyclosporine with or without methylprednisolone. Transplantation. 1985;40(2):162-6
16. Cutler C, Li S, Ho VT, Koreth J, Alyea E, Soiffer RJ, et al. Extended follow-up of methotrexate-free immunosuppression using sirolimus and tacrolimus in related and unrelated donor peripheral blood stem cell transplantation. Blood. 2007;109(7):3108-14.
17. Benito AI, Furlong T, Martin PJ, Anasetti C, Appelbaum FR, Doney K, et al. Sirolimus (rapamycin) for the treatment of steroid-refractory acute graft-versus-host disease. Transplantation. 2001;72(12): 1924-9.
18. Couriel DR, Saliba R, Escalon MP, Hsu Y, Ghosh S, Ippoliti C, et al. Sirolimus in combination with tacrolimus and corticosteroids for the treatment of resistant chronic graft-versus-host disease. Br J Haematol. 2005;130(3):409-17.
19. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report. Biol Bone Marrow Transplant. 2005;11(12):945-55.
20. Wolff D, Gerbitz A, Ayuk F, Kiani A, Hildebrandt GC, Vogelsang GB, et al. Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. Biol Blood Marrow Transplant. 2010;16(12):1611-28.
21. Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M, et al. Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. Biol Blood Marrow Transplant. 2011;17(1):1-17.
22. Kharfan-Dabaja MA, Mhaskar AR, Djulbegovic B, Cutler C, Mohty M, Kumar A. Efficacy of rituximab in the setting of steroid-refractory chronic graft-versus-host disease: a systematic review and meta-analysis. Biol Blood Marrow Transplant. 2009;15(9):1005-13.
23. Paczesny S, Krijanovski OI, Braun TM, Choi SW, Clouthier SG, Kuick R, et al. A biomarker panel for acute graft-versus-host disease. Blood. 2009;113(2):273-8.