



## Chronic GVHD: Established and Emerging Therapies

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### Definitions and Staging

Chronic GVHD is the main long-term complication and limitation to successful hematopoietic stem cell transplantation (HSCT). It affects over 50% of all patients undergoing HSCT, and the majority of those with acute GVHD(1). It has a major impact both in quality of life as well as survival. Chronic GVHD frequently involves multiple organs, and requires prolonged immunosuppressive therapy(2). In one report, 15 % of cancer-free patients were still on immunosuppressive therapy after 7 years(3). The more severe forms of chronic GVHD are clearly associated with a lower disease-free survival. Thus, the potential benefit of a graft-versus-leukemia effect is shadowed by significant treatment-related mortality(4).

Chronic GVHD is a disease of deregulated immunity with protean manifestations similar in many ways to autoimmune diseases. The relative uncommonness of the disease, the lack of consensus on what represents true manifestations of chronic GVHD, the very limited understanding of its pathophysiology, and the clinical complexity of these patients are all factors that have hindered a systematic approach to the treatment of this problem. It is important to recognize chronic GVHD is a distinct clinical syndrome, different from acute GVHD, or the autoimmune disorders it mimics. This has been recently recognized by the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD (5). Thus, as in the case of acute GVHD, the definition of chronic GVHD is eminently clinical. Although the vast majority of cases of chronic GVHD will occur after the classical "100 day" boundary, this should not be part of the definition of chronic GVHD, particularly since it is relatively common to see cases of "late" acute GVHD(6, 7) Strategies that have successfully prevented acute GVHD, such as reduced-intensity preparative regimens, seem to have less or no impact on the incidence of chronic GVHD. Approximately one third of patients without a history of acute GVHD will have de novo chronic GVHD<sup>8</sup>. On the other hand, not all patients affected by acute GVHD will go on to develop chronic GVHD. Chronic GVHD mimics some aspects of autoimmune conditions like systemic lupus erythematosus or scleroderma. However, the clinical differences here may be just as significant as the similarities. Thus, chronic GVHD is a relatively

“autonomous” entity, and the nature of its association with acute GVHD or similarities with other autoimmune disorders remain unclear.

## **Treatment of Chronic GVHD**

### General Aspects and Initial Therapy

Chronic GVHD is a multisystem disorder that most frequently affects multiple organs, and well as psychosocial and sexual aspects of an otherwise cancer-free patient. The involvement of multiple organs dictates the need for a multidisciplinary approach, coordinated by the transplant physician, preferably at a center that has experience in the care of these patients. Larger transplant centers have organized clinics devoted to the follow-up and care of long-term HSCT complications, including GVHD. The participation of sub specialists with an interest, and ideally experience with chronic GVHD patients is always desirable as well.

There are 2 aspects to the management of chronic GVHD, both equally important and interdependent(8): systemic management with immunomodulatory agents and ancillary and supportive care.

### Systemic Therapy

Systemic treatment with immunosuppressant and immunomodulating agents. Corticosteroids administered with a calcineurin inhibitor such as cyclosporine or tacrolimus have been and remain the single most effective therapy(9). Although there may be no advantage in the combination with cyclosporine, this may reduce the long term complications of corticosteroids, possibly acting as a steroid-sparing agent (10). The alternative use of tacrolimus with corticosteroids does not seem to offer any additional advantage in the initial treatment of chronic GVHD(11). The median duration of immunosuppressive therapy for patients with chronic GVHD is approximately 2 years (3), and non-relapse mortality may be increased in patients receiving higher doses of prednisone immediately before the diagnosis of chronic GVHD (3). Additionally, the long-term complications of corticosteroid therapy, like myopathy and avascular necrosis of the bone, are relatively frequent in this patient population (12-14). On occasion these steroid-related complications can become more problematic than chronic GVHD itself.

It is still unclear whether “intensifying” initial therapy by incorporating new agents to the initial combination of calcineurin inhibitor plus corticosteroid results in better responses, quality of life or survival. Based on their efficacy in the treatment of steroid-refractory chronic GVHD, different agents were incorporated

as initial treatment. In a study by Sullivan et al, the addition of azathioprine to prednisone did not result in any improvement (15). Arora et al evaluated thalidomide in combination with cyclosporine and prednisone, and the results of this study were no different than those of prednisone alone (16). A recent study by Martin et al evaluated the addition of mycophenolate mofetil (MMF) to corticosteroids for the initial treatment of chronic GVHD in a double-blind, randomized, multicenter study (17). The addition of MMF did not improve the treatment results when compared to patients receiving prednisone alone. Furthermore, the MMF group seemed to have a tendency to a higher rate of thrombocytopenia, recurrent malignancy and death.

Overall, the response rate to initial therapy with corticosteroids is about 50% (15, 16), including complete and partial responses. Thus, there is a high proportion of patients that will be exposed to the long term effects of corticosteroids, in whom the need for salvage therapy with steroid-sparing potential is essential.

#### Overview of Most Commonly Used Steroid-Sparing Therapies

A variety of new drugs and other immunomodulatory treatments have shown activity in the salvage therapy of chronic GVHD. This evidence originates in small pilot and phase II studies, with doses and schedules usually matching those of their FDA approved use. Thalidomide, sirolimus, extracorporeal photopheresis (ECP), rituximab, pentostatin, mycophenolate mofetil, hydroxychloroquine and clofazimine are some examples(2, 6, 18, 19). The overall response to salvage therapy has ranged between 30 to over 70%. Unfortunately, with all these different therapies, the vast majority of these responses are partial, and their corticosteroid sparing effect has not been systematically assessed or reported(8). In addition to the difficulties inherent to the assessment of response in chronic GVHD, it is likely that a substantial proportion of the patients included in chronic GVHD studies that used a chronological definition may have had "late" acute GVHD.

The toxicity of some of these regimens, such as thalidomide(16), or the combination of sirolimus and tacrolimus (6) can be substantial.

As for initial salvage therapy, this still remains to be determined. An organ-based choice is the usual approach. For example, in chronic GVHD of the skin, active options include thalidomide (20), sirolimus (6), rituximab (18) and ECP (19). Cases with a predominant sclerotic form of cutaneous chronic GVHD are particularly responsive to clofazimine (21) and also ECP, sometimes over a long period of therapy (19, 22). Patients with lichenoid forms have also responded to light therapy with PUVA (23).

The evaluation of the role of newer immunomodulating, rather than immunosuppressant therapies, aimed at facilitating or inducing immune tolerance is under way.

### Ancillary and Supportive Care

The second component of chronic GVHD therapy, occasionally overlooked, is ancillary and supportive care (24). This includes education, prevention of flares, infectious disease prophylaxis, physical and occupational therapy, nutrition, alleviation of the chronic manifestations of GVHD and its treatment, and providing the patient with coping mechanisms or resources to deal with the psychosocial, sexual and financial consequences of the disease. These interventions, when successful, may have the potential to reduce the need for systemic therapy, and the relative impact of these interventions on the outcome of patients with chronic GVHD needs to be explored.

Initial treatment with corticosteroids can control chronic GVHD in about 50% of the patients, and the majority of those without resolution of their chronic GVHD will also suffer the consequences of prolonged immunosuppression (3)

### Supportive Care and Ancillary Interventions:

Although usually neglected or forgotten as we are struggling with more than one marginally ineffective systemic therapies, this should be as important a component in the care of patients with chronic GVHD. Although we know the impact of interventions such as education in photo protection, physical therapy, prevention of osteoporosis has a positive impact, we still do not have an accurate idea to what extent these relatively nontoxic therapies have relatively to systemic immunosuppression. Therefore, the main questions are whether “intensive” supportive care can contribute to less flares, steroid sparing, less adverse effects from systemic immunosuppression, a better quality of life, and ultimately survival (24).

## Conclusions

Despite our better understanding of histocompatibility and recent advances in transplant immunology, GVHD and its complications continue to be the major limitation to successful allotransplantation. We hope that newer immunomodulatory strategies will make a difference as prophylactic strategies or very early in the course of acute GVHD. Once established, particularly in forms that are not readily responsive to steroids, acute GVHD has a dismal prognosis. Chronic GVHD is a different disease, and prevention of acute GVHD does not naturally lead to a lower incidence of chronic GVHD. Since the clinical redefinition

of chronic GVHD by the NIH Consensus Conference, a new baseline has been set for the systematic development of clinical trials that will hopefully provide a better understanding of risk factors, prognosis and therapy. The initial treatment of chronic GVHD continues to be corticosteroids with calcineurin inhibitor, and so far no other strategy can be recommended outside a clinical trial. Since a substantial proportion of patients will require long-term corticosteroid treatment, the search for salvage therapies that are active in the treatment of established chronic GVHD with a steroid-sparing effect still continues. The area of ancillary and supportive care has recently regained new interest, possibly due to the fact that most of our interventions for these patients tend to belong to this category, particularly in patients who have advanced and severe forms of the disease. The impact of these interventions on systemic therapy, and particularly their steroid-sparing effect is also an emerging area of interest

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