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Have we made progress in the management of chronic graft-vs-host disease?

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Abstract

Chronic graft-vs-host disease (GVHD) is a common long-term complication of allogeneic hematopoietic cell transplant that is associated with very high morbidity and mortality. In order to understand whether we have made progress in the management of chronic GVHD, it is helpful to first propose a definition of meaningful “progress.” The following can be considered to be indicators of improved management of chronic GVHD: a decrease in the incidence or severity of chronic GVHD, better efficacy or decreased toxicity of therapies, better quality of life despite chronic GVHD, and improved overall and disease-free survival rates. However, to date, real progress has not been made in these areas, though there are promising new preventive strategies and treatments. Furthermore, a consensus has been reached in the research community about many different issues surrounding chronic GVHD definitions, management, and the conduct of clinical trials. These consensus documents will help to standardize efforts and data collection so that true comparisons can be made in the future and real clinical progress achieved.

Keywords

chronic graft-vs-host disease; allogeneic hematopoietic cell transplantation; quality of life; survival; incidence

INTRODUCTION

Chronic graft-vs-host disease (GVHD) is the most common long-term complication of allogeneic hematopoietic cell transplant (HCT).¹ It affects 30%–70% of all allogeneic HCT recipients who survive for 100 days, with a median onset of 4–6 months after HCT. Most cases are diagnosed within the first year of HCT, but 5%–10% of cases are diagnosed beyond one year. Clinically, this syndrome has both inflammatory and fibrotic components. The signs and symptoms can vary between individuals and in the same individual over time. It is a multisystem complication, and about 50% of patients have 3 or more involved organs.

Chronic GVHD is associated with very high morbidity and mortality. This results in an increased medical burden, both for the patient and for society. For example, patients with

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Conflict of interest statement

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chronic GVHD have continued need for immunosuppressive medications. The median time of treatment is between 2 and 3 years after chronic GVHD diagnosis, with 15% of patients needing immunosuppressive therapy even 7 years after diagnosis.² Chronic GVHD is associated with more frequent and severe infections, and 60%–85% of deaths in patients with chronic GVHD are attributed to infections. Chronic GVHD is associated with worse patient-reported outcomes, including significantly lower health-related quality of life, worse functional status (40%–50% report significant deficits³), and an inability to go to work or reassume their social roles. Furthermore, chronic GVHD is the leading cause of non-relapse mortality in 2-year disease-free survivors. In patients receiving transplant for a malignant disorder, there is around a 10% absolute survival difference at 10 years for those with chronic GVHD vs those without.^{4,5} For those who receive HCT for a nonmalignant disorder, there is an even bigger difference in absolute survival because there is no beneficial graft-vs-leukemia effect. In aplastic anemia, for example, the difference in absolute survival is 20%; at 20 years, the overall survival for patients without GVHD is 89% vs 69% in those with GVHD.⁶

PROGRESS IN CHRONIC GVHD

Meaningful progress in the management of chronic GVHD could potentially be indicated by a number of measures: lower incidence or severity of chronic GVHD, more effective or less toxic therapies, better quality of life despite chronic GVHD, or better survival or disease-free survival. Better survival might be achieved if the graft-vs-leukemia effect can be harnessed while managing complications and symptoms.

Lower incidence or severity of chronic GVHD

Most randomized studies have not shown any benefit of treatments to prevent chronic GVHD,^{7–15} and a study of thalidomide prophylaxis showed that those who received thalidomide did worse.¹⁶ The two chronic GVHD prevention strategies that have shown benefit in previous randomized trials, the use of antithymocyte globulin (ATG) as GVHD prophylaxis^{17,18} and the use of granulocyte colony-stimulating factor (G-CSF) stimulated bone marrow as the graft source¹⁹ are now being tested in larger definitive studies by the Canadian Blood and Marrow Transplant group. Other interesting approaches to prevent chronic GVHD include the use of umbilical cord blood and posttransplant treatment with cyclophosphamide^{20,21} as acute GVHD prophylaxis. While early phase II studies look promising, more data are still needed on these approaches.

It is unclear from the literature whether the rate of chronic GVHD is increasing or declining. At the Fred Hutchinson Cancer Research Center, Barry Storer has analyzed data from 1980–2006 on 5050 patients who had received allogeneic transplant and survived at least 100 days free of their malignancy (unpublished data). While the rate of chronic GVHD increased from 1985–2000, this might be explained by an increase in unrelated donor transplants, the switch from bone marrow to peripheral blood transplants, and the increasing age of transplant recipients. The rate decreased from 2000–2006, but this is probably due to a redefining of chronic GVHD based on the National Institutes of Health (NIH) Consensus Development Project on criteria for clinical trials in chronic GVHD. Six different groups came up with consensus definitions of diagnosis and scoring,²² pathology,²³ biomarkers,²⁴ response criteria,²⁵ supportive care,²⁶ and clinical trials.²⁷

While some of these definitions were controversial, a consensus was reached on all issues. However, some of these changes interfered with the ability to analyze chronic GVHD trends. For example, in the diagnosis and staging group, the definition of acute and chronic GVHD was changed, affecting who would and would not be included in the cohort of people with chronic GVHD. Previous to the NIH Consensus Conference, acute GVHD was

considered to be alloimmunity from day 1 to day 100 after graft infusion, while any GVHD after day 100 was categorized as chronic (Figure 1a). This definition made data management easy but led to clinical confusion, as a patient who experienced symptoms on day 99 would be called acute and then switched to chronic on day 101 even without any change in symptoms. The NIH revision created two new groups of patients: late acute and overlap (Figure 1b). Retrospective reviews of population data show that 10%–48% of patients who were previously called chronic are now considered acute, and a group of previously classified chronic patients are now being considered “overlap” patients where features of both acute and chronic GVHD are present.^{28–31} This new reclassification may decrease the numbers of chronic GVHD patients by as much as 50%.

The definition of chronic GVHD severity has also changed, but the amount of organ involvement has stayed consistent over the last several decades, with a few slight differences that may be due to changes in diagnostic criteria.

More effective or less toxic therapies

Primary therapies do not seem to be more effective or less toxic, with most new therapies showing no benefit. There have been multiple randomized studies^{32–39} that brought agents that seemed to be helpful in the steroid-refractory setting to the upfront setting, but these studies were mostly negative, with several closing early due to interim analyses suggesting futility or due to low enrollment.^{35,36,38,39} The standard initial treatment remains prednisone 0.5–1.0 mg/kg per day with or without a calcineurin inhibitor (CNI).

In the study by Martin et al comparing mycophenolate mofetil (MMF) to placebo after corticosteroid-based initial therapy,³⁹ 151 patients of a target of 230 were enrolled. The trial was stopped early because of futility. Final analyses showed the rate of chronic GVHD resolution was similar in both arms, but the rate of treatment failure, defined by death or having to be treated with secondary agents, was higher for the MMF arm. Furthermore, patients on the MMF arm had almost twice the death rate compared to the placebo arm. This study suggests that overtreating GVHD might have a negative effect on survival.

The literature shows that there are 30 agents (Table 1) that have some efficacy in chronic GVHD, although 3 of those are not yet approved for any uses. The salvage response rate has been reported between 20% and 82%, although different levels of dosing and endpoint assessment have been used to evaluate these agents. In the last several years, 5 agents have emerged from the rest. Extracorporeal photopheresis (ECP), MMF, rituximab, and sirolimus are the most popular therapies for steroid-refractory chronic GVHD, and imatinib mesylate has generated enthusiasm based on recent studies.

The Blood and Marrow Transplant Clinical Trials Network has opened a phase II/III study with a target population of 500 high-risk and poorly responding standard-risk patients with chronic GVHD. If this study is completed, it will be the largest study of chronic GVHD ever performed. The study is testing two approaches to increase T-regulatory cells (T-regs) in vivo and will have 3 arms: all arms will receive prednisone and sirolimus, the comparator arm will receive prednisone, sirolimus, and a calcineurin inhibitor (CNI); another arm will only receive prednisone and sirolimus; while the third will receive prednisone, sirolimus, and ECP. This design will allow investigators to determine whether CNIs are interfering with T-regs and if ECP is enhancing them.

Other potential new agents are more targeted and nuanced, as opposed to pan T-cell inhibitors that are currently used. New agents of interest include tyrosine kinase inhibitors such as imatinib, a PDGFR inhibitor, and the related medications, nilotinib, and dasatinib. Due to evidence that B-cell dysregulation, including high B-cell activating factor (BAFF)

levels, has a role in the pathophysiology of chronic GVHD, the BAFF antibody belimumab is of interest. This agent is currently being studied for lupus and may seek FDA approval soon. A number of antifibrotic agents are being investigated, including halofuginone, a collagen type 1 inhibitor, which has been used in sclerotic GVHD. Initial studies are reporting emerging data on cellular therapies, such as T-reg infusions or mesenchymal stem cell infusions.

Better quality of life

It is hard to tell whether quality of life for people with chronic GVHD is improving, because studies require longitudinal assessments using comparable instruments. However, it is clear that there is much room for improvement. Patients with active chronic GVHD have many quality of life and functional deficits.³ Around 40% of patients with active chronic GVHD have deficiencies in their general health and mental health and experience regular pain. About 50% of patients with active chronic GVHD report functional impairment and activity limitation, while 20% report anxiety. These measures, when combined, show that more than 80% of patients with chronic GVHD report quality of life or functional deficits.

The NIH Consensus conference has the ability to help improve quality of life for two reasons: (1) one of the consensus papers focused on supportive and ancillary care,²⁶ which reflects a greater interest and enthusiasm in helping patients with symptom alleviation and functional status, even independent of the natural history of the disease; and (2) the conference recommended a battery of patient-reported outcomes for clinical studies. A number of ongoing studies in Canada and the US will be using the same instruments at approximately the same time points in their studies, which will enable researchers to measure improvements in quality of life and allow comparisons across studies.

Better survival or disease-free survival

Data from the Fred Hutchinson Cancer Research Center on patients who have been diagnosed with chronic GVHD show that there has not been any significant, meaningful improvement in overall or relapse-free survival. The rates of 2-year (after diagnosis) overall survival and relapse-free survival have fluctuated from around 60% to 80% between 1980 and 2006.

Conclusions

Has progress been made in the management of chronic GVHD? Based on the four criteria outlined above, not much definitive progress has been made, although there is hope for the future. While the incidence and severity of chronic GVHD has not decreased, several randomized trials are hoping to show a lower rate of chronic GVHD and are based on previous randomized trials that showed positive outcomes. Current therapies are not more effective or less toxic, but some promising therapies are in clinical trials, and there are others on the horizon. New therapies may target the pathophysiology of chronic GVHD, as opposed to the pan-immunosuppressive agents currently available. It is difficult to tell whether quality of life despite chronic GVHD has improved, but new studies will include standard patient-reported measures that will enable better analysis in the future. Finally, overall and disease-free survival has not improved yet, but we seem to be on the cusp of making progress. There is real national and international collaboration, the same instruments and measurement tools are being used in clinical studies, and there is communication among groups. It appears likely that in the near future a more encouraging progress report on the management of GVHD will be made.

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A.

B.

Figure 1.

Visual representations of former and current definitions of acute and chronic GVHD. A) Former definition.²² B) Revised NIH consensus definition.^{28–31}

Table 1

List of 30 agents used in secondary therapy for chronic GVHD. Agents marked with an open circle represent agents that have emerged among the group.

•	Acitretin/etretinate
•	Alefacept
•	Alemtuzumab
•	Antithymocyte globulin
•	Azathioprine
•	Bortezomib
•	Clofazimine
•	Daclizumab
•	Extracorporeal photopheresis (ECP)
•	Etanercept
•	Halofuginone
•	Imatinib
•	Infliximab
•	Interleukin-2
•	Lidocaine
•	Mesenchymal stem cells (MSC)
•	Methotrexate
•	Montelukast
•	Mycophenolate mofetil
•	Pentostatin
•	Pravastatin
•	Psoralen/UVA
•	Rituximab
•	Sirolimus
•	Steroids (pulse)
•	Thoraco-abdominal radiation
•	T-regulatory cell infusions
•	Thalidomide
•	Ursodeoxycholic acid
•	UVB