Improved Therapeutic Approaches Are Needed to Minimize the Burden of Graft-Versus-Host Disease

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Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) offers a potentially curative therapy for patients suffering from diseases of the hematopoietic system but requires a high level of expertise and is both resources intensive and expensive.

A frequent and life-threatening complication after alloHSCT is graft-versus-host disease (GvHD), and GvHD treatment places a significant burden on patients and healthcare resources, but data on costs are scarce.

Acute GvHD (aGvHD) generally causes skin, gastrointestinal and liver symptoms, while chronic GvHD (cGvHD) has a different pathophysiology and may affect nearly every organ or tissue of the body.

Failure of the alloHSCT, for whatever reason (e.g. GvHD, malignant disease relapse or graft failure) leaves the patient with a poor prognosis and few options for potentially successful salvage treatment.

Objectives

Health policy makers and payers have a limited knowledge and understanding of alloHSCT and in particular the impact of GvHD on patient outcomes (quality of life (QoL) and their long-term survival) and costs.

The purpose of the analysis is to raise awareness of the GvHD economic burden and the need for new and scientifically proven and cost-effective treatments to maximize successful outcomes.

Methods

A targeted literature review studied GvHD in alloHSCT, to examine patient burden and especially the impact of GvHD on QoL.

The economic burden, considering the impact on healthcare resource utilization and costs, and the current and potential treatments were analyzed.

Results

GvHD is the most life-threatening complication following alloHSCT. Despite the administration of GvHD prophylaxis, between 39% and 59% of patients develop aGvHD and approximately 36–37% of patients develop cGvHD.

Table: Summary of graft-versus-host disease (GvHD) in allogeneic haematopoietic stem cell transplantation (alloHSCT)[1]

Type of GvHD	Percent of alloHSCT recipients developing GvHD	Percent developing GvHD by grade	Survival with GvHD by grade	Mortality with GvHD	Percentage of GvHD patients developing refractory GvHD
aGvHD	39% with sibling donors 59% with unrelated donors 49%	12% grade II 11-16% grade III–IV	91% 100-day overall survival (OS) grade II 65% 100-day OS grade III-IV 86% 1-year OS grade III-IV 79% 2-year OS grade III-IV 29% 3-year OS grade III-IV 38% 1-year OS grade IV	16.2% aGvHD (5.3% without GvHD) 8-16% 49% grade IV aGvHD 1-year treatment-related mortality (TRM)*	36% grade II-IV steroid-refractory aGvHD
cGvHD	36% 37%	19% grade 2 8% grade 3	82%, 73% and 71% OS with moderate to severe cGvHD at 1, 2 and 3 years respectively 53% 3-year OS 45% 5-year OS	35% TRM* (11% without cGvHD) 8-11% 3-year mortality	31% all grades steroid-refractory

Note: AlloHSCT outcomes are dependent on multiple factors making it difficult to provide generally applicable ranges, especially when considering recent trends of improved alloHSCT procedures and regimens. Relevant factors include recipient age, patient fitness/co-morbidities, underlying malignant/non-malignant disease, graft source, donor type/age, conditioning regimen, pre alloHSCT treatment, GvHD prophylaxis and post alloHSCT treatment.
*Treatment- (or Transplant-) related mortality defined as death unrelated to relapse or disease progression.

GvHD is associated with high mortality rates and approximately 80% of patients with refractory aGvHD die. However, GvHD may not always be fatal and the morbidity it causes places a heavy burden on the patients and the healthcare teams through their survivorship. Post-alloHSCT, GvHD is currently the most challenging issue for physicians to manage. The table below illustrates a summary of the percentage of alloHSCT recipients developing GvHD and refractory GvHD and the associated mortality/survival.

In HSCT survivors, GvHD is a major determinant of long-term quality-of-life (QoL). Patients who develop GvHD show a profound and lasting decline in their QoL compared to those who do not develop GvHD.

Systemic steroids are used first-line for GvHD but response decreases with disease severity which in turn leads to an increase in non-relapse mortality.

GvHD has a significant impact on healthcare resource utilization, with patients experiencing more and longer hospitalization significantly raising post-alloHSCT cost and incurring a financial burden on healthcare systems.

A study in the USA found significantly greater 1-year post-alloHSCT costs for patients with aGvHD compared to those without aGvHD ($466,720 vs. $263,568; $P < 0.001$), with inpatient care being the primary cost driver.[2] A Swedish real-world study showed that the cumulative direct medical costs over 3 years post-alloHSCT for patients with moderate-to-severe cGvHD were approximately fourfold higher than for patients without cGvHD.[3]

Increased GvHD disease severity significantly increases post-alloHSCT costs. This may be because increasing severity indicates steroid-resistant GvHD. Such steroid-resistant GvHD had been shown to double patient costs compared to those without GvHD. The mean total initial hospitalization costs of patients with aGvHD who were either steroid-resistant or high risk were $205,880 compared to $97,417 for those with no aGvHD as reported in a US retrospective claims database analysis. For patients with steroid-resistant cGvHD, mean total costs were $532,673 versus no cGvHD costs of $252,909 in the 2 years following alloHSCT in another US retrospective claims database analysis.[4,5]

For second-line and subsequent lines of therapies for GvHD, a wide range of pharmaceutical agents are currently recommended. However, there is no accepted standard-of-care treatment and the treatment choice is generally down to physician experience rather than clinical and economic evidence. With new and ongoing trials, the treatment landscape in Europe is expected to change, with new options becoming available and current second-line therapies becoming third and subsequent lines of therapies. For steroid-refractory patients, physicians may add in another therapy in combination with steroids.

Conclusions

To ensure optimal benefit from alloHSCT, the long-term goal is to prevent or control GvHD, preserving the beneficial effects of the graft and minimizing the costs of an expensive but life-saving therapy.

Treatments to improve long-term post-transplant outcomes remain an unmet need. Improving and expanding the clinical and economic evidence base should be a high priority when investigating new therapeutic agents.

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