Diagnostic Methods to Predict Outcomes for Acute Graft Versus Host Disease in Allogeneic Hematopoietic Cell Transplant Recipients

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Accurate and early identification of patients at high-risk for severe acute graft versus host disease (aGVHD) and related complications has the potential to improve patient outcomes following allogeneic hematopoietic cell transplantation (allo-HCT). High-risk patients can be preemptively treated for aGVHD prior to the onset of clinical disease while low-risk patients may potentially avoid unnecessary treatment. Validation of an interpretive algorithm based on serum ST2 and REG3α levels accurately predicts risks for allo-HCT patients when testing is performed at 7 days post-transplant, at the onset of aGVHD symptoms, and ≥ 1 week after the initiation of systemic therapy.

KEY POINTS:

- **Algorithmic interpretation of ST2 and REG3α levels allow risk stratification of allo-HCT patients**
- **Knowledge of an individual patient's risk status provides an objective basis for adjusting immunosuppressive doses**
- **Interventional studies are underway to evaluate the efficacy of treatment modifications**

Introduction

Acute graft versus host disease (aGVHD) is the major cause of non-relapse mortality following allogeneic hematopoietic cell transplantation (allo-HCT) and an important limitation to more widespread use of allo-HCT. Acute GVHD primarily affects skin, liver and the gastrointestinal tract in the first two to three months post-HCT and occurs in 40 – 60% of allo-HCT patients. Efforts to reduce aGVHD-related morbidity and mortality are focused on predicting aGVHD prior to onset in an attempt to block the full development of clinical disease by adjusting immunosuppressive drug dosages (Harris et al., 2012). Until recently, progress towards this goal has been minimal.

Acute GVHD occurs when donor T lymphocytes react with proteins on host cells. The pathophysiology is complex and is typically initiated by conditioning regimens which damage host tissue leading to release of pro-inflammatory cytokines (e.g. TNF-α, IL-1 and IL-7) and activation of antigen presenting cells (APCs). The APCs activate donor T cells with the end result of recipient cell apoptosis. The risk of aGVHD is determined by a number of factors: degree of HLA match between donor and recipient, recipient age, donor type (related or unrelated) and conditioning regime intensity (Jagasia et al., 2012; Harris et al., 2013).

Current (standard) diagnosis of aGVHD relies almost entirely on the presence of clinical symptoms in one or more of the main target organs (skin, liver, gastrointestinal tract), with subsequent confirmation by biopsy of the involved target organs. However, the shortcomings of this approach are very significant: the symptoms of aGVHD are often non-specific and can be confused with other common etiologies (including infectious complications), biopsy results may be inconclusive, and perhaps most importantly, waiting for the onset of clinical signs and biopsy results allows significant disease progression and thus eliminates the possibility of preemptive treatment.

Due to the inadequacy of current aGVHD diagnostic approaches, work over the past several years has investigated the use of biomarkers for non-invasive and ideally predictive assessment of aGVHD risk. A number of promising biomarkers have been identified (Paczesny, 2013). Clinical use of these, and other biomarkers, has been limited due to a lack of clinical validation, with well-established cutoff values for specific patient groups, and standardization between laboratories.

Recent Advances Leading to Improved Diagnostics

Recently an analysis algorithm based on measurement of two key biomarkers, ST2 and REG3α, in serum was shown to predict NRM and aGVHD before the development of clinically apparent aGVHD (Hartwell et al., 2017). Based on this algorithm, high- and low-risk groups were assigned from analysis of samples collected 7 days post-HCT. Donor type, HLA-match/mismatch, intensity of conditioning and age of recipient did not influence the ability to distinguish high- from low-risk patients. Both non-relapse mortality and overall survival were significantly worse in the high-risk group. Additionally, GVHD mortality and the occurrence of severe GI and skin GVHD was significantly more frequent in high-risk than low-risk groups; patients in the high-risk group were three times more likely to die from GVHD than low-risk patients.

Furthermore the same algorithm, based on ST2 and REG3α blood levels, used at the onset of GVHD clinical signs, defined risk groups for response to treatment and NRM (Hartwell et al., 2017). For this use, two diagnostic thresholds assign patients to three risk groups corresponding to Ann Arbor (AA) risk groups 1, 2 or 3 for low, intermediate and high risk, respectively. Patients below the lower threshold (Ann Arbor 1) had 6 month NRM rates three-fold lower than AA2 and five-fold lower than AA3 groups.

Analysis of samples through the same algorithm was further applied to risk stratify steroid-resistant patients ≥1 week after the initiation of systemic treatment for GVHD (Major-Monfried et al., 2018). A third set of clinical cutoffs was applied to these patients. Results of the algorithm separated steroid-resistant patients into two risk groups (high or low) for NRM and overall survival (OS). Although resistance to steroids and GVHD severity (Minnesota index) were also predictors of NRM, results of the algorithm had a significantly higher area under the curve (AUC) following receiver operator characteristic curve analysis. The key outcome-based results are summarized for each application in **Table 1** and clinical use is illustrated in **Figure 1** (see page 3).

Table 1. Summary of results derived from algorithm analysis of ST2 and REG3α levels

Sample collection time	Risk group assigned by algorithm	Non-relapse mortality	Overall Survival	Acute GVHD incidence
7 days post-transplant (before symptoms)	High	29%[1]	62%[1]	18.14%
	Low	8%[1]	84%[1]	4.43%
Onset of clinical signs (before treatment)[2]	High	46%	-	-
	Intermediate	24%	-	-
	Low	8%	-	-
Steroid-resistant patients after ≥1 week of treatment	High	67%[3]	27%[3]	-
	Low	18%[3]	73%[3]	-

[1]Weighted average of non-relapse mortality (NRM) at 6 months and overall survival (OS) from training (N=620), test (N=309) and validation (N=358) cohorts.

[2]N=57, 59, and 96 for high, intermediate and low risk groups, respectively.

[3]Weighted average of NRM at 12 months and OS from test (N=122), validation 1 (N=80) and validation 2 (N=68) cohorts.

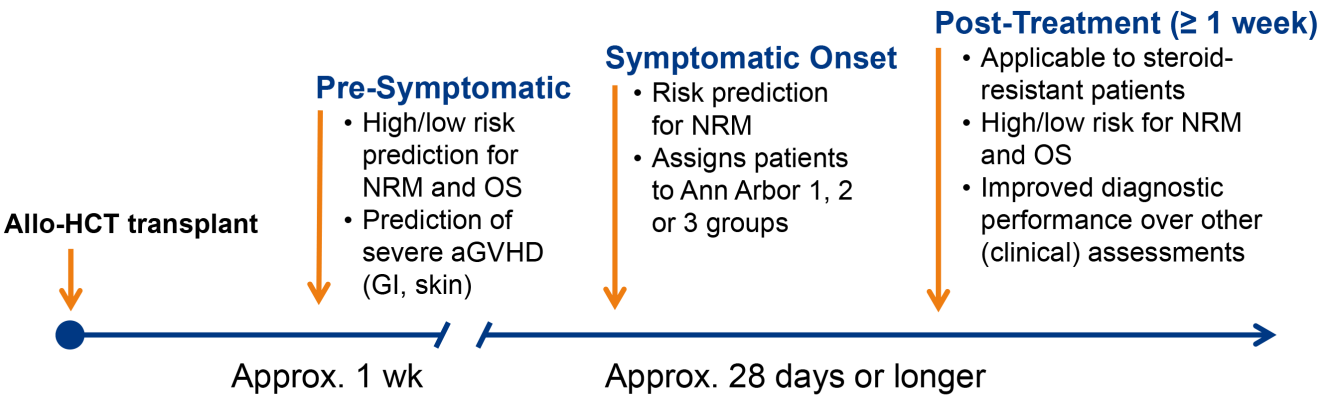

Figure 1. Potential applications and timing for use of a predictive algorithm (based on ST2 and REG3α levels) for patients at risk for acute graft versus host disease (aGVHD). HCT, Hematopoietic Cell Transplant; NRM, non-relapse mortality; OS, overall survival.

Summary

Acute GVHD is a major complication following allo-HCT. Diagnosis has long been limited to clinical signs and biopsy results. Recently an algorithm based on serum levels of ST2 and REG3α has been validated to improve both diagnosis and prognosis for these patients. Application of clinically validated cutoffs has allowed stratification of patients into risk categories at 7 days post-transplant, at the onset of clinical signs (but before treatment) and following ≥1 week of systemic treatment. Knowledge of a patient's individual risk will allow adjustments to therapy with a goal of improved outcomes.

References

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