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Biomarkers for Early Complications After Hematopoietic Stem Cell Transplantation

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SUMMARY

The advancement in technology, particularly in the field of omics, has led to numerous discoveries of biomarkers for early post-HSCT complications. Future research must include the testing of newly discovered biomarkers against existing, validated biomarkers. Work also needs to be done to implement the promising, validated biomarkers into clinical practice in a time-efficient and cost-effective manner. The prognostic biomarkers should be incorporated into clinical trials so that the effect of early recognition on the outcomes of HSCT recipients can be assessed. Diagnostic biomarkers can help to differentiate the complex variety of diseases that can be present in this population. Finally, biomarkers that can serve as therapeutic targets should be further studied. Many of these post-HSCT complications have limited or nonspecific therapeutic options. For example, corticosteroids are the first-line therapy for aGVHD. Using biomarkers to help identify underlying biologic pathways may open new therapeutic avenues that deserve investigation. This major advancement in technology allows for early diagnosis of complications, risk stratification for complications, and potential new therapeutic targets. All of these strides can improve the utilization of life-saving allogeneic HSCT while minimizing complications and mortality.

Keywords

Biomarkers; Hematopoietic stem cell transplantation; Proteomics; Graft versus host disease

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is increasingly being used for a variety of malignant and nonmalignant conditions. With improvements in donor selection and conditional regimens, outcomes have improved. However, early posttransplant complications

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remain a barrier for overall success and survival. Issues such as acute graft-versus-host disease (aGVHD), sinusoidal obstructive syndrome (SOS), and idiopathic pneumonia syndrome (IPS) can dramatically increase morbidity and mortality. For example, up to one-half of patients who have undergone allogeneic HSCT can be affected by aGVHD[1] and are at increased risk for mortality.

Biomarkers can offer an effective method for early identification of complications related to HSCT and potentially guide treatments. Biomarkers have gained popularity over the years as a way to provide objective, unbiased information. As technology has advanced, there has been an explosion in the development and applications of biomarkers in an array of specialties. These markers can be obtained from a variety of medical samples, such as blood and urine, but can also be thought of in the broader sense to include data such as radiographic images obtained from use of other technologies. An ideal biomarker would be obtained from a readily available, noninvasive sample that could be easily collected at multiple time points. Currently, plasma and serum remain the most common sources for biomarkers and effectively provide information on systemic disorders that often affect the transplant recipient, such as aGVHD.

In a National Institutes of Health–sponsored working group, biomarkers were categorized into 4 types: diagnostic, prognostic, predictive, and response to treatment[2] (Table 1). A diagnostic biomarker helps a clinician identify a disease rapidly or differentiate between diseases with similar presentations. A prognostic biomarker should aid a clinician in the anticipated course of a disease or the development of a particular complication. A predictive biomarker gives information about how a patient or disease progression will likely respond to a specific treatment, therapy, or intervention when measured before the treatment. Finally, a response to treatment marker can be used to monitor the treatment response and could substitute for a clinical response endpoint. Unlike a predictive marker, it is measured after treatment is initiated to monitor therapeutic response.

OMICS TECHNOLOGIC ADVANCES AND THE DEVELOPMENT OF BIOMARKERS

The recent technologic advances combined with their decreasing cost have led to a rapid increase in the application of omics in translational research and then in clinic. There are many different types of omics, but the most popular remain genomics, transcriptomics, and proteomics. The foundation of the omics field was built on genomics, which is the study of how genetic variants are associated with disease development or prognosis. In addition, it is being increasingly applied to stratify patients at risk for adverse events to certain drugs (ie, pharmacogenomics). Transcriptomics measure gene activity by investigating the messenger RNA that codes for different proteins. Proteomics investigates protein quantity and function. It is important because it measures both gene function and the host environment, but is complicated due to the sheer volume of proteins. These omics all carry different importance. For this review, the authors focus on the most relevant and recent biomarkers that have been validated in different cohorts.

The development of a biomarker is complicated and involves many steps from discovery to implementation in the routine clinical care of patients. Fig. 1 highlights the important steps of development. These steps must all be followed to ensure the validity and clinical utility of newly discovered biomarkers.

BIOMARKERS FOR EARLY COMPLICATIONS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

Acute Graft-Versus-Host Disease

aGVHD is one of the best studied post-HSCT complications because it remains a major barrier to the overall success of this procedure. Because the presentation is diverse and the diagnosis relies entirely on clinical symptoms, there has been a quest to develop and validate biomarkers to aid in early diagnosis and prognosis. Furthermore, many of these biomarkers are being developed as potential novel therapeutic targets. Table 2 features an overview of the most recent and validated biomarkers for aGVHD.

Genomic markers for the development and severity of aGVHD following HSCT have been investigated. In addition to the well-known risk of major histocompatibility complex disparity,[3] single nucleotide polymorphisms (SNPs) for mismatches in minor histocompatibility antigens have also been found to be risk factors for the occurrence of aGVHD, and increasing genome-wide recipient mismatching results in a substantial increased risk for grades III–IV GVHD.[4] Genomic markers remain complicated to investigate because of the need to understand the genome of the donor and the recipient pre-HSCT and after HSCT, and the small effect of each SNP requires large cohorts of thousands of HSCT patients to get meaningful and reproducible data.[5]

Recent transcriptomics analysis in the nonhuman primate have found that blocking OX40L using the blocking antibody KY1005 helped to control Th1 cells while preserving the reconstitution of regulatory T cells (Tregs) and prolonged GVHD-free survival. There was an additional benefit when combined with sirolimus.[6] This antibody is currently being tested in a clinical trial through the Pediatric Blood and Marrow Transplant Consortium.

A variety of proteomic markers have been studied, and the most validated and recent ones are presented in Table 2. Several of the interleukins and their receptors (IL-2, IL-2Rα, IL-6, IL-8, IL-12, and IL-18) have been investigated, and IL-2Rα and IL-6 have emerged as the most useful markers for aGVHD.[7–9] Using a screen of patient plasma samples by competitive hybridization to arrays of antibodies specific for diverse proteins, the first biomarker panel for aGVHD, including 4 different proteins IL-2Ra, tumor necrosis factor receptor 1 (TNFR1), IL-8, and hepatocyte growth factor (HGF), was identified and validated in a training and validation set of hundreds of patients.[9] Although Denileukin Diftitox, an anti-IL-2Rα antibody, did not show benefit for the treatment of aGVHD,[10] IL-6 has been more promising for prophylaxis against aGVHD. The use of tocilizumab in a phase 1/2 trial demonstrated a decrease in occurrence of aGVHD but no overall survival advantage.[7] Stimulation 2 (ST2), the IL-33 receptor, is a marker that has been discovered through an unbiased tandem mass spectrometry approach and has been validated in several cohorts as a

diagnostic, prognostic, predictive, and response to treatment biomarker.[8,11–17] It has been tested in a variety of patients with different conditioning, transplant donor source, and degrees of match.[11,12] As early as day 7 or 14 after HSCT, it can serve as a prognostic marker for aGVHD and nonrelapsed mortality.[8,14,18] Furthermore, it may be a promising therapeutic target. ST2 blockade in murine models has demonstrated the ability to decrease the severity of GVHD and associated mortality.[19]

Cellular markers have also been studied, including Tregs, CD146T cells, CD30, and invariant natural killer T cells.[20–23] CD146-expressing T cells and upregulation of CCR5 (a chemokine receptor) were found to be prognostic for gastrointestinal (GI) GVHD as early as day 14 after HSCT.[22] A phase 1 clinical trial for brentuximab vedotin, an antibody-drug targeting CD30, has been tested for steroid-refractory aGVHD. In this trial, there was almost a 40% response rate with 15% achieving complete remission.[24]

Organ-specific markers have also been discovered. Elafin, which is overexpressed in inflammatory skin disorders, was found to be associated with the diagnosis of skin GVHD.[25] GI and liver GVHD markers include HGF, cytokeratine-18 fragments (KRT18), T-cell immunoglobulin domain and mucin domain (TIM-3), and regenerating isletderived 3-α (REG3α), with REG3 α emerging as the most validated biomarker specifically for GI GVHD with prognostic ability.[26–28] Recently, hypothesis-driven markers such as amphiregulin have emerged. Amphiregulin, an epidermal growth factor receptor ligand, was found to accurately define patients with a high-risk Minnesota aGVHD risk score, and to predict steroid responsiveness and nonrelapsed mortality (NRM).[29]

Sinusoidal Obstruction Syndrome

SOS, previously known as veno-occlusive disease, is a serious post-HSCT complication that affects the sinusoidal endothelial cells of the liver. It has been reported to occur in up to 13% of HSCT recipients, and when severe, is associated with multiorgan failure and significant mortality.[30] The diagnosis of SOS remains challenging because it is dependent mostly on clinical presentation and supported with blood work showing elevated bilirubin and ultrasound results of the liver demonstrating reversal of the hepatic flow.

Although many markers of coagulation, such as antithrombin, thrombomodulin, protein C, von Willebrand factor, and plasminogen activator inhibitor-1, have been found to be associated with SOS in early studies,[31–33] these markers are nonspecific and have not been well validated in current HSCT populations. Given the endothelial involvement, markers of endothelial dysfunction have been investigated. Using state-of-the art proteomics, a panel of 5 proteins (angiopoietin 2 [Ang2], hyaluronic acid [HA], vascular adhesion molecule-1 [VCAM-1], ST2, and L-ficolin) has been identified and validated with diagnostic value. All biomarkers were found to be elevated with the exception of L-ficolin, which was reduced.[34] HA and VCAM-1, combined with L-ficolin on day 0 of HSCT, is an early prognostic panel of markers for SOS[34] (Table 3).

Pulmonary Complications

Pulmonary complications remain a significant source of early transplant-related mortality. Part of the difficulty in treating post-HSCT pulmonary disease is the diverse infectious and

noninfectious causes that are difficult to understand, diagnose, and treat. Complications, such as IPS, require ruling out infectious causes before the institution of more specific IPS therapy. To that end, diagnostic markers for IPS have recently been identified. IL-6 and ST2 are good diagnostic markers for IPS, and TNFR1 is able to distinguish IPS from underlying viral causes.[35] This same group of biomarkers has been investigated for general respiratory failure, which carries up to a 60% mortality in this population.[36] ST2 and IL-6 on day 7 after HSCT were found to be great prognostic markers for the future development of respiratory failure in an adult and pediatric cohort.[37] However, these findings need to be validated in an independent cohort. Biomarkers for pulmonary complication offer the benefit of not only early prognosis but also a method to understand potential underlying biology of the disease process and offer new therapeutic targets.

Other Early Transplant Complications

Biomarkers for other early post-HSCT complications have also been investigated. Posttransplant diabetes mellitus (PTDM) has been reported in both pediatric and adult patients who have undergone allogeneic HSCT.[38] There is an association with hyperglycemia in adults after HSCT and the occurrence of GVHD and overall mortality.[39,40] As such, early identification and institution of therapy are important for this population. A large adult cohort revealed that elevated ST2 was associated with PTDM.[41] This association held when investigated in an isolated pediatric cohort.[42]

Thrombotic microangiopathy (TMA) is a post-HSCT complication associated with endothelial injury and complement activation that can lead to increased mortality and morbidity.[43] Many organs can be affected leading to multiorgan dysfunction and death. Diagnosis of this disease is challenging because of lack of uniformed acceptance of diagnostic criteria.[44] Discovery of specific biomarkers may lead to improved therapeutic decisions. Recently, ST2 on day 14 after HSCT has been found elevated in patients with TMA.[45]

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KEY POINTS

- Biomarkers should be categorized into diagnostic, prognostic, predictive, and response to treatment biomarkers based on the 2014 National Institutes of Health consensus report.
- Several proteomic biomarkers for acute graft-versus-host disease have been investigated by unbiased or hypothesis-driven approaches. Stimulation 2 has been the most validated and is a promising therapeutic target.
- Discovery of additional biomarkers for other posttransplant complications is ongoing and may improve diagnosis, prognosis, and the development of new therapeutic strategies.

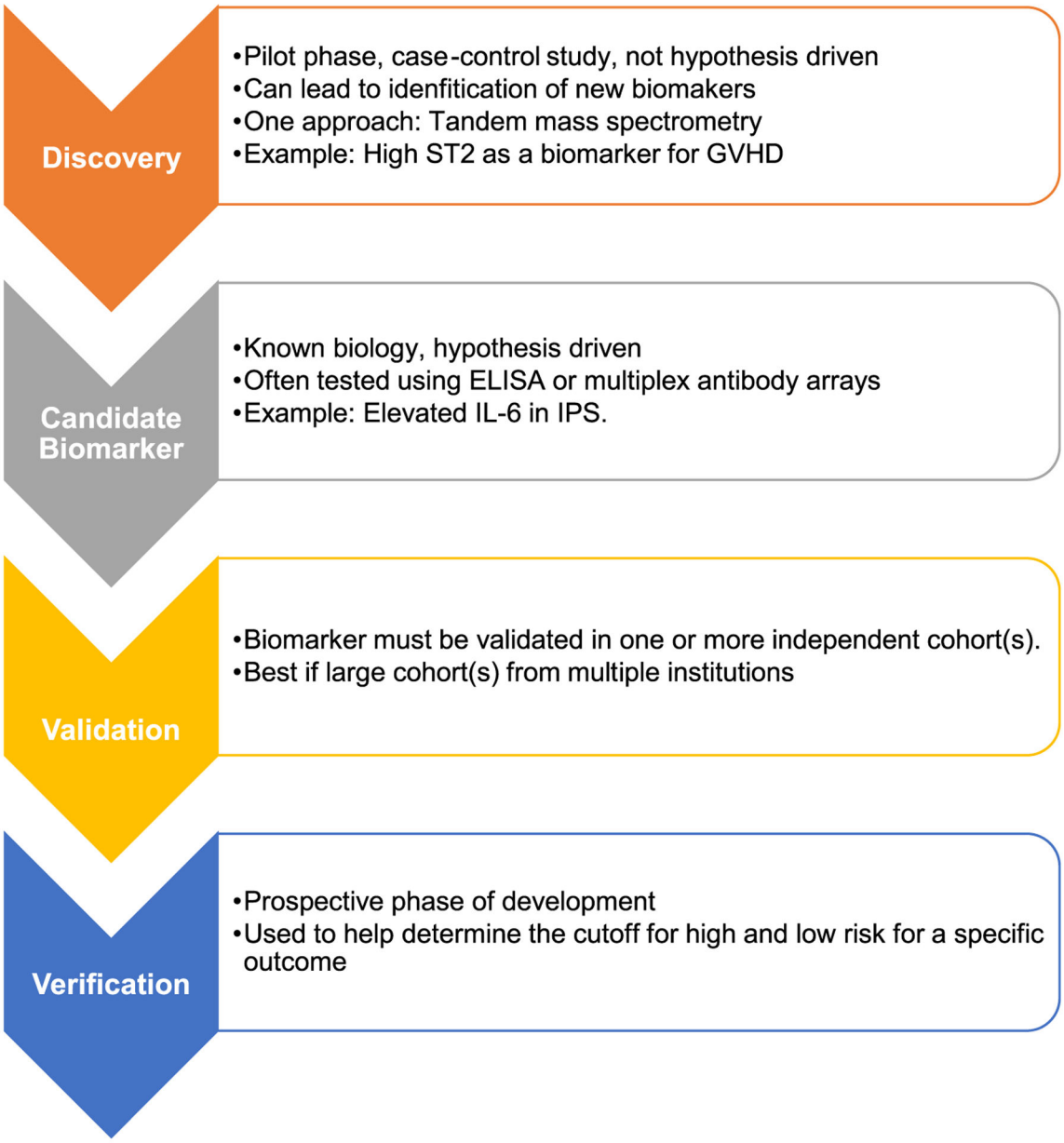

Fig. 1.

There are several steps involved in the development of a biomarker for clinical use. The first step is a discovery phase that usually compares 20 to 40 cases and controls. This is often done with mass spectrometry. Candidate biomarkers are biomarkers that are often chosen based on biologic plausibility. Studies of candidate biomarkers are hypothesis driven. These markers often are in the early phases of study and lack extensive validation. Once a newly discovered biomarker demonstrates promising statistical association, validation must be performed. This is usually done using high-throughput immunoassay. The cohorts should be independent, and the validation is stronger if the cohort is large and from multiple

institutions. Finally, the biomarker should be verified. This is often done in large prospective studies that can help to determine cutoffs for high or low risk for a specific outcome.

Table 1

Categories of biomarkers as defined by the National Institutes of Health working group

Category	Definition	Example
Diagnostic	• Can help a clinician identify a disease rapidly so that treatment can be initiated • Can help to differentiate diseases with similar clinical presentations	REG3α can help to differentiate Gl GVHD from other causes of non-GVHD diarrhea[28]
Prognostic	• Can aid the clinician in the anticipated course of disease • Can also help determine the likelihood of developing a particular complication	A panel of HA, VCAM, and L-ficolin drawn on day 0 of HSCTcan serve as a prognostic panel for the future development of SOS[34]
Predictive	• Measured before therapy is initiated • Helps to determine how a disease will progress following therapy • Can give information on how a patient will respond to a particular treatment of intervention	ST2 can serve as a predictive marker for response to therapy for GVHD[14]
Response to treatment	• Measured after therapy is initiated • Can help monitor therapeutic response • Could potentially be used as a substitute for a clinical response	MAGIC biomarkers (ST2 and Reg3α) measured at 1 wk after initiation of steroids can predict steroids resistant disease and nonrelapsed mortality[16]

Table 2

Biomarkers for acute graft-versus-host disease

Name	Study	(n)	Biomarker Type	Associations and Time Points in aGVHD
Plasma markers				
4 biomarker panel: IL-2-receptor-α, HGF, IL-8, TNFR1	Paczesny et al,[9] 2009	424	• Diagnosis • Prognostic	• Can discriminate patients with GVHD at onset of clinical symptoms • Prognostic abilities for severity of GVHD
lnterleukin-6 (IL-6)	Kennedy et al,[7] 2014	48 patients: phase 1/2 clinical trial	• Therapeutic target	• Prophylactic tocilizumab given to adults undergoing allogeneic HSCT had decreased incidence of aGVHD
	McDonald etal,[8]2015	74 training cohort	• Diagnostic	• Increased at onset of aGVHD
		76 validation cohort	• Prognostic	• Associated with severity of GVHD and NRM
ST2	Vander Lugtet al,[14] 2013	673 in total from 3 independent sets	• Predictive	• Increased level at 14 d after HSCT predicts response to aGVHD treatment and 6-mo mortality
	McDonald et al,[8] 2015	74 training cohort	• Diagnostic	• Increased at onset of aGVHD
		76 validation cohort	• Prognostic	• Associated with severity of GVHD and NRM
		167 patients without GVHD		
	Levineetal,[46]2015	328 training set	• Predictive	• Increased levels predictive of NRM from aGVHD
		164 test set		
		300 validation set		
	Abu Zaidetal,[15] 2017	211 patients (independent cohort of previously identified biomarkers)	• Predictive	• Increased levels on day 28 after HSCT were associated with NRM
	Hartwell et al,[18]2017	620 training set	• Prognostic	• Increased day 7 were prognostic for development of aGVHD and NRM
		667 validation set		
	McDonald etal,[17]2017	165 patients with aGVHD	• Response to treatment	• ST2 combined with TIM3 measured on day 14 of steroid therapy can predict response to treatment

Name	Study	(n)	Biomarker Type	Associations and Time Points in aGVHD
	Major-Monfried et al,[16] 2018	236 test set	• Response to treatment	• ST2 combined with REG3α (MAGIC biomarkers) measured at 1 wk after initiation of steroids can predict steroid refractory disease and NRM
		142 validation set		
		129 validation set		
TIM3	McDonald etal,[8]2015	74 training set	• Diagnostic	• Increased at onset of aGVHD
		76 validation set	• Prognostic	• Associated with severity of GVHD and NRM
		167 patients without GVHD		
	AbuZaid etal,[15]2017	211 patients (independent cohort of previously identified biomarkers)	• Predictive	• Increased levels on day 28 after HSCT were associated with NRM
Amphiregulin	Holtan et al,[29] 2018	251 patients with aGVHD	• Prognostic risk score	• High levels (>33 pg/mL) could refine risk categories within the Minnesota aGVHD clinical risk score • Associated with NRM and response to steroids
Skin specific				
Elafin	Paczesny etal,[25]2010	522: discovery	• Diagnostic	• Diagnostic ability for skin GVHD
		492: validation	• Prognostic	• Associated with severity of disease and NRM
	Bruggen et al,[47]2015	59	• Prognostic	• Elevated levels in skin are associated with poor prognosis of skin GVHD
GI specific				
REG3α	Ferraraetal,[28]2011	20 discovery	• Diagnostic	• Elevated at onset of GI aGVHD
		1014 validation set	• Predictive • Prognostic	• Level at onset predicts response to aGVHD treatment and NRM
	Harris et al,[27] 2012	954 patients, 3 centers	• Diagnostic	• Best biomarker to discern GI GVHD from non-GVHD diarrhea
TIM3	Hansen etal,[26]2013	20: discovery set	• Diagnostic	• Levels elevated in those with GI aGVHD prior onset of clinical symptoms

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Name	Study	(n)	Biomarker Type	Associations and Time Points in aGVHD
		127: validation set	• Prognostic	
		22: validation set		• Increased levels associated with severity of gut GVHD
Liver specific				
REG3α, HGF, and KRT18	Harris et al,[27] 2012	954 patients, 3 centers	• Diagnostic	• Elevated in patients with liver GVHD, not validated due to low incidence
Cellular markers				
Regulatory T cells	Magenau et al,[21] 2010	215	• Diagnostic • Predictive	• Lower Tregs in peripheral blood are associated with aGVHD • Tregs frequency at GVHD onset were predictive on response to therapy
CD146+T cells	Li et al,[22] 2016	20 discovery set	• Prognostic	• Increased T cells expressing CD146 at day +14 after HSCT was associated with increased risk for Gl GVHD
		214 validation set		
CD30	Chen etal,[23] 2012	53	• Diagnostic	• Elevated CD30 levels at the time of clinical presentation of aGVHD
	Chen etal,[24] 2017	34	• Clinical trial	• Phase 1 trial of brentuximab vedotin, antibody drug for CD30, found to have 38% response rate in steroid-refractory Gl aGVHD
Invariant natural killer T cells	Chaidos etal,[20] 2012	57	• Prognostic	• High levels in donor graft was associated with a decrease in the development of GVHD

Abbreviation: NRM, nonrelapsed mortality.

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Table 3

Biomarkers for sinusoidal obstructive syndrome after HSCT

Name	Study	(n)	Biomarker Type	Associations and Time Points in SOS
Ang2, HA, L-ficolin, ST2, VCAM	Akil et al,[34] 2015	40 discovery 45 training set 35 validation	Diagnostic	• Composite panel for the diagnosis of SOS • All markers increased except L-ficolin, which is decreased
HA, L-ficolin, VCAM	Akil et al,[34] 2015	Derived from cohort above	Prognostic	• Prognostic panel at day 0 of HSCT for the development of SOS • All markers increased except L-ficolin, which is decreased
L-ficolin	Abu Zaid etal,[15] 2017	211	Prognostic	• Low level on day 28 was associated with the development of SOS