The predictive value of specific biomarkers in acute and chronic GvHD after allo-HSCT

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This article is based on recent findings by Chung *et al.*,[1] and Wang *et al.*,[2] where specific biomarkers were analyzed in order to predict the incidence and severity of graft-versus-host disease (GvHD). For allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients, acute (aGvHD) and chronic GvHD (cGvHD) are associated with considerable non-relapse related mortality (NRM). Both retrospective studies aimed to identify protein markers that predicted the development of GvHD and subsequent outcomes in these patients.

aGvHD following allo-HSCT

Lower gastrointestinal (GI) tract aGvHD is a frequent form of the disease characterized by diarrhea and abdominal pain, as the most common symptoms. Even though corticosteroids are the standard prophylactic immunosuppressant treatment, about half of the patients do not respond, leading to a poor prognosis with an increased risk of NRM. In order to correctly stage the severity of lower GI aGvHD, obtaining accurate stool volume measurements is vital. However, since this has to be done with patients in a hospital setting, stool volume measurements are usually inaccurate and unreliable. Thus, identifying potential biomarkers related to the development of lower GI aGvHD can help to better manage these patients and consider alternative treatment strategies.

Brief study design

The study by Chung *et al.*,[1] retrospectively assessed data from 244 acute leukemia patients from a single institution, who received allo-HSCT. Of those patients, 100 developed aGvHD after allo-HSCT with 48/244 (19.7%) patients being diagnosed with

lower GI aGvHD. Diagnosis of lower GI aGvHD was based on stool volume and endoscopy with histopathology. Patients with aGvHD were treated with systemic corticosteroids. Treatment response was determined on Days 7, 14 and 28 and classified as complete response (CR), partial response (PR), progressive disease (PD) or no response (NR). Any patient determined with PD or NR at any given time was allocated at Day 28 to the corticosteroid-resistant group. Serum albumin and C-reactive protein (CRP) levels were measured at least twice weekly to determine the Glasgow Prognostic Score (GPS). See **Table 1**.

Table 1. Allocation of GPS score[1]

GPS	**Serum albumin**	**CRP**
Low	Normal	
Intermediate	Low albumin ***or*** high CRP	
High	Low (< 3.3g)	High (≥ 10mg/L)
CRP, C-reactive protein; GPS, Glasgow Prognostic Score		

Statistical analysis was performed with chi square and *t* tests to assess differences between the groups for categorical and continuous variables, respectively. Response to corticosteroids and NRM was analyzed by univariate and multivariate logistical regression.

Results

Of the 48 patients (19.7%) diagnosed with lower GI aGvHD, 20 (41.6%) were resistant to first-line corticosteroid therapy. Univariate analysis showed that corticosteroid resistance was associated with advanced stage of lower GI aGvHD (grade 3–4; p= 0.001), concomitant skin aGvHD (p= 0.036), low albumin on Day 7 (< 3.3g/dL; p= 0.001), high CRP on Day 7 (≥ 10mg/L; p= 0.001). All except concomitant skin aGvHD remained significant response markers in the multivariate analysis.

When these patients were classified according to GPS, 13 had a low GPS, while 11 had intermediate and 18 high GPS. In the high GPS group, the rate of corticosteroid resistance was significantly higher (83.3%) compared to those with intermediate (27.2%) and low GPS (15.3%; p< 0.001). Similarly, the two-year NRM rate was 62.2% in the high GPS group, while it was only 31.4% in the intermediate GPS group and 0% in the low GPS group. This led to significantly better NRM rates in the low GPS group than in the intermediate (p= 0.031) or high GPS group (p< 0.001).

Multivariant analysis showed that serum albumin (p= 0.046) and CRP levels (p= 0.032) on treatment Day 7 were independent prognostic factors for NRM.

In conclusion, this study showed that low serum albumin and high CRP one week after systemic corticosteroids predicted a higher NRM and were determined to be valid biomarkers for corticosteroid resistance in patients with lower GI aGvHD. Since this was a retrospective study from a single center, more studies are warranted to further confirm these findings.

cGvHD following allo-HSCT

A retrospective study by Wang *et al.*,[2] investigated the predictive value of free light chains (FLC) in serum after allo-HSCT for the development of cGvHD. As with aGvHD, worsening cGvHD leads to poor prognosis and is associated with a higher risk of NRM. Unlike aGvHD where skin, liver and GI tract are the predominant target organs, cGvHD may involve more organs. Studies have shown that cGvHD is associated with delayed reconstitution of B lymphocytes. Nevertheless, predicting cGvHD remains difficult and many markers have been shown to be either unreliable or impractical in

normal clinical practice. Therefore, there is an unmet need for reliable and easy to measure predictive biomarkers for cGvHD that could help initiate more and earlier intensive treatment options.

Brief study design

Clinical data was retrospectively collected from 62 patients at a single hospital who underwent an allo-HSCT.

The median age of patients was 31 years (range, 1–54 years) and had one of the following diagnoses: acute myeloid leukemia (n= 28), acute lymphoblastic leukemia (n= 18), myelodysplastic syndrome/myeloproliferative diseases (n= 13), non-Hodgkin lymphoma (n= 2) and one case of severe aplastic anemia. Half of the patients (50%) had a high-risk disease status and 35 patients developed aGvHD (grade 1–2, n= 24; grade 3–4, n= 9 patients).

Both aGvHD and cGvHD were graded based on ongoing grading criteria and in accordance with the current National Institute of Health (NIH) grading system. Analysis of factors associated with FLC levels and cGvHD risk factors was assessed by univariate and multivariate logistical regression.

Results

Independently, 30 patients were shown to be below the detection level for κ-FLC or λ-FLC, while 18 patients were below the detection limit for both, κ- and λ-FLCs, and were subsequently defined as the low-level group, while the rest were categorized to the high-level group (n= 44). Blood samples were collected at a medium of 31 days post allo-HSCT (range, Day 25^{+} to Day 42^{+}). Regression analysis showed that sampling time had no influence on FLC serum levels (p= 0.576).

Investigating factors that could affect the level of FLC, such as gender, age, estimated glomerular filtration rate (eGFR), donor age, disease status, conditioning regimen, donor sources, the mononucleated and $CD34^{+}$ cell dose or time of neutrophil and platelet engraftment were not independent factors of FLC levels, as revealed by multivariate analysis.

Overall, 33 patients (53.2%) developed cGvHD, with 14 patients presenting with extensive lesions based on the Seattle cGvHD diagnostic criteria. According to the NIH severity score, 17 patients had mild cGvHD, six had moderate cGvHD and 10 had severe cGvHD.

Disease status (p= 0.024) was identified as an independent risk factor for cGvHD with both univariate and multivariate analyses. FLC levels were not a risk factor for all severity stages of cGvHD. Only low serum FLC levels were able to predict the development of extensive or moderate-to-severe cGvHD based on both the univariate and multivariate analyses (multivariate data: p= 0.01 and p= 0.038, respectively). There was no statistical difference in the overall survival between the low and high FLC level groups.

Conclusion

Identifying risk factors that have significant predictive values following allo-HSCT can greatly improve treatment strategies and enable the better management of aGvHD and cGvHD. Currently, transplant-related mortality and associated complications remain a considerable challenge for these patients. Further investigation into these biomarkers will help with outcome prediction but also improve treatment and subsequently the overall survival of this patient population.

References:

1. Chung H. et al. Serum albumin and C-reactive protein as significant predictors of non-relapse mortality in lower gastrointestinal graft-versus-host disease. *Ann Hematol.* 2020 Apr 6. DOI: 1007/s00277-020-04015-4

2. Wang B. et al. The predictive value of serum free light chain level early after allogeneic hematopoietic stem cell transplantation for chronic graft-versus-host disease, a preliminary study. Clinical Transplantation. *Clin Transpl.* 2020 Apr 3. DOI: 1111/ctr.13865

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