

Validation of Minnesota acute graft-versus-host disease Risk Score

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Diagnosis, Staging and Grading of GVHD

Signs and symptoms of acute GVHD were graded by the Minnesota grading system which uses standard clinical criteria derived from organ staging(1) modified to include upper gastrointestinal (GI) acute GVHD per the GVHD consensus conference.(2-4) Grade of GVHD refers to clinical (not histologic) grade throughout this report. Initial grade was calculated using the maximum stage in each organ within a 14 day window (-7 to day +7) mostly prior to initiation of steroid therapy. For the majority (91%) of patients, the maximum stage was determined within a 10 day window (day -7 to +3) after initiation of steroids. For 32 patients (9%), the maximum stage was calculated from staging recorded at days +4 to +7). Prospective real-time organ staging and grading of GVHD was determined weekly by the attending physician, supported by laboratory and clinical information and histologic confirmation when possible. All patients' GVHD diagnoses and maximum GVHD staging were retrospectively reviewed and adjudicated by the Acute GVHD Scoring Committee (MLM, DJW, SGH and AR). The overall grade used for this analysis was determined by a computer algorithm, incorporating all available clinical and pathologic GVHD organ staging data as originally and prospectively recorded. Responses at weekly or biweekly endpoints were determined by review of the prospectively recorded staging and grading data.

Response was determined by reviewing the maximum acute GVHD stage in each organ over a window time frame at days 14 (± 7 days), 28 (± 7 days) and 56 (± 14 days) after prednisone treatment was initiated. Complete response (CR) was defined as the complete resolution of acute GVHD symptoms in all organs, without secondary GVHD therapy. Partial response (PR) was defined as improvement in GVHD stage in all initial GVHD target organs without complete resolution, without worsening in any other GVHD target organs, and without secondary GVHD therapy. No response (NR) was defined as the same grade of GVHD in all affected organs, or death, or the addition of secondary GVHD therapy. Progression was defined as worsening GVHD in ≥ 1 organ with or without improvement in any organ. Steroid resistant acute GVHD was

defined as progression of acute GVHD after 4 days of treatment with prednisone or no improvement after 7 days of treatment. Patients with steroid resistant GVHD were treated with secondary therapy and were considered to have no response. If patients experienced a flare of acute GVHD and required therapy with a boost of steroids or additional GVHD therapy, they were also considered to have no response.

Supportive Care

Broad-spectrum prophylactic antibiotics was prescribed in all patients. Patients received acyclovir prophylaxis if they were seropositive for herpes simplex virus and/or cytomegalovirus (CMV). Oral trimethoprim-sulfamethoxazole was given for pneumocystis jiroveci pneumonia prophylaxis. CMV-seronegative recipients received CMV-safe (seronegative or filtered) blood products. Additional intravenous antibacterial and, as indicated antifungal and antiviral antimicrobials were used when patients developed fever.

Statistical Analysis

Univariate assessment of various factors on response at days 14, 28 and 56 after initiation of steroid therapy was performed by the Chi-square test. Overall survival after treatment was estimated by Kaplan-Meier curves.(5) TRM and the competing risk of relapse or death due to disease were analyzed using cumulative incidence.(6) Comparisons were completed with the Log-Rank or Gray's test. Assessment of day 28 response on endpoints was performed in a similar manner, but with landmark analyses excluding deceased patients (2%) prior to the day 28 assessment.(7) The Minnesota acute GVHD risk score was the primary factor of interest. Pre-specified potential confounding and clinically significant factors were also included in the regression models. These factors included age (<18 vs. 18-35 vs. 36-59 vs. 60+ years), HCT-comorbidity index score (CI; 0 vs. 1-2 vs. 3+), donor type (sibling vs. matched URD vs. mismatched URD vs. single UCB vs. double UCB) and time from HCT to steroid treatment (continuous). Conditioning [myeloablative (MA) vs. reduced intensity conditioning (RIC)] was

included as a stratification factor in the models primarily due to violation of the proportional hazards assumption. Logistic regression was used to examine the independent effect of factors on the endpoint of response. Cox regression was used to assess the independent effect of factors on two-year overall survival.(8) Fine and Gray proportional hazards regression was used to assess the independent effect of factors on TRM.(9) All reported p-values were 2-sided. All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) and R version 3.5.1.

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