Impact of posttransplantation G-CSF on outcomes of allogeneic hematopoietic stem cell transplantation


Granulocyte colony-stimulating factor (G-CSF) is often administered after hematopoietic-cell transplantation (HCT) to accelerate neutrophil recovery, but it is unclear what impact G-CSF has on long-term transplantation outcomes. We analyzed within the database of the Center for International Blood and Marrow Transplant Research the impact of giving posttransplantation G-CSF on the outcomes of allogeneic HCT for acute myelogenous leukemia and chronic myelogenous leukemia in 2719 patients who underwent transplantation between 1995 and 2000.

Patients, materials, and methods

Data source

The CIBMTR is a voluntary working group of more than 400 transplant centers worldwide that contribute detailed data on consecutive allogeneic HCT to a Statistical Center at the Health Policy Institute of the Medical College of Wisconsin in Milwaukee. Approximately 40% of all allogeneic HCTs worldwide are registered with the CIBMTR. Participating centers are required to register all transplantations consecutively; compliance is monitored by on-site audits. Patients are followed.
longitudinally, with yearly follow-up. Computerized checks for errors, physician reviews of submitted data, and on-site audits of participating centers ensure data quality.

The CIBMTR collects data at 2 levels: Registration and Research. Registration data include disease type, age, sex, pretransplantation performance status, disease stage and chemotherapy responsiveness, date of diagnosis, donor and graft characteristics (bone marrow—and/or blood-derived stem cells), conditioning regimen, engraftment, graft-versus-host disease (GVHD), disease recurrence, development of secondary malignancies, survival, and cause of death. Data on disease or death for registered patients are requested at 6-month intervals. All CIBMTR teams contribute Registration data on all patients. Research data include very comprehensive pre- and posttransplantation clinical information and are collected only on subsets of registered patients selected using a weighted randomization scheme.

**Patient selection**

The patient population consisted of unmanipulated HLA-identical matched sibling or unrelated allogeneic hematopoietic cell transplant recipients with chronic myeloid leukemia (CML) or acute myeloid leukemia (AML) who underwent transplantation between 1995 and 2000 and whose data were reported to the CIBMTR. A total of 6108 cases registered with the CIBMTR were identified. Of these, 2719 patients with AML or CML with full Research data who received bone marrow (BM) or peripheral-blood stem cells (PBSCs) from an HLA-identical sibling or BM from an unrelated donor (URD) were selected for analysis. Recipients of URD PBSC transplants were excluded from this analysis. The population was restricted to patients receiving myeloablative conditioning regimens, methotrexate and cyclosporine with or without other drugs for GVHD prophylaxis, and who had no prior transplantation. Those who received nonmyeloablative or reduced-intensity conditioning were excluded. Graft failure was defined as failure to achieve an ANC higher than 0.5 \( \times 10^9/L \) for at least 3 consecutive days, a decrease in the ANC to less than 0.5 \( \times 10^9/L \) (500/\( \mu L \)) for at least 3 consecutive days after initial engraftment, or documentation of the loss of donor cells. To ensure that patients with Research data were a representative subset of all registered patients, demographic characteristics and survival of patients were compared according to type of graft; no differences were noted. Patients were divided into 3 cohorts according to type of hematopoietic-cell transplant: HLA-identical sibling BM (n = 1435), URD BM (n = 675), and HLA-identical sibling PBSC (n = 609) transplants. Donor and recipient HLA matching were defined using low-resolution typing methods; and only 6 of 6 matched related or unrelated donor transplants are included in this analysis. Each cohort was further divided into those who received posttransplantation G-CSF (G-CSF+) within 7 days (between days 0 and +7) after HCT and those who did not receive G-CSF or who received G-CSF more than 7 days after HCT (after day +7; G-CSF−). The cutoff time of 7 days was determined based on the analysis of data obtained from centers that “routinely” administer G-CSF (to >80% of their patients). Indeed, with the 7-day cutoff, only 3% of patients would have engrafted, suggesting that 97% of patients received G-CSF to hasten neutrophil recovery. However, although a day-14 cutoff captures more patients who received posttransplantation G-CSF (90% vs 75% for the 7-day cutoff), 10% of BM, 37% of PBSCs, and 14% of URD would have engrafted, which leads to selection bias in a Registry analysis (G-CSF administered for indications other than for neutrophil engraftment).

**Study end points**

Primary outcomes were grades II to IV acute GVHD and chronic GVHD in patients surviving more than 90 days with evidence of engraftment. Other clinical outcomes evaluated include the following: neutrophil engraftment (defined as an absolute neutrophil > 0.5 \( \times 10^9/L \) [500/\( \mu L \)] for 3 consecutive days after initial nadir), duration of hospitalization after transplantation, day-30 and day-100 survivals, overall survival, leukemia-free survival (LFS, survival in continuous complete remission), and treatment-related mortality (TRM). TRM is defined as death in continued remission; patients were censored at relapse, or for those in continuous remission, at last follow-up. For LFS, patients were considered treatment failures at the time of relapse or death from any cause; all living patients were censored at the last follow-up evaluation.

**Statistical analysis**

Patient-, disease-, and transplantation-related variables were compared between G-CSF+ and G-CSF− cohorts according to type of allograft, using the Chi-square test for categoric variables and the Wilcoxon test for continuous variables. Univariate probabilities of LFS and overall survival were calculated using the Kaplan-Meier estimator; the log-rank test was used for univariate comparisons. Probabilities of acute or chronic GVHD, leukemia recurrence, and TRM (at days +30, +100, and 1 and 3 years) were calculated using cumulative incidence curves to accommodate competing risks. We compared the clinical outcomes of patients who received or did not receive G-CSF within 7 days after transplantation according to allograft type using Cox proportional hazards regression. This allowed us to adjust for the influence of the following variables (Table 1): age, sex, Karnofsky performance score at transplantation, disease type (AML vs CML), disease status at transplantation (early vs intermediate vs advanced), use of total body irradiation (TBI) as part of conditioning, donor-recipient sex match, year of transplantation, and type of GVHD prophylaxis on the various study end points being studied. To evaluate the bias created by including patients who received G-CSF after 7 days after HCT in the G-CSF− group, similar models were constructed eliminating the patients who initiated G-CSF therapy more than 7 days after HCT. The assumption of proportional hazards was tested using a time-dependent covariate. Administration of G-CSF (yes vs no) was forced in all the models, with no G-CSF considered as the baseline or reference group in all models. Forward stepwise variable selection at a 0.05 significance level was used to identify other covariates associated with outcome. Interactions between G-CSF administration and all covariates were tested before and after model building. Overall covariate effects were tested using the Wald test. All computations were executed using the procedure PHREG in the statistical package SAS V8 for Unix (SAS Institute, Cary, NC).
Results

Patients

Patient characteristics are summarized in Table 2. Nineteen percent, 35%, and 40% of BM, PBSC, and URD BM recipients, respectively, received posttransplantation G-CSF, as previously defined. The patient-, disease-, and transplantation-related characteristics in G-CSF+ or G-CSF− cohorts were comparable in age, sex, Karnofsky performance score at transplantation, disease stage, donor and recipient CMV status, donor-recipient sex match, use of TBI for conditioning, and median follow-up time of survivors. BM recipients who did not receive G-CSF in the HLA-identical sibling and unrelated cohorts were more likely to have CML; and URD recipients receiving TBI were less likely to receive posttransplantation G-CSF. Median time of start of G-CSF was 5 days (range, 0–7 days), 3 days (range, 0–7 days), and 6 days (range, 0–7 days) in the BM, PBSC, and URD BM groups, respectively.

Neutrophil engraftment and hospitalization

The number of patients who experienced graft failure was comparable within each cohort (5% vs 6% for G-CSF− and G-CSF+ BM, respectively; 3% vs 3% for G-CSF− and G-CSF+ PB, respectively; and 7% vs 5% for G-CSF− and G-CSF+ URD BM, respectively). Median time to neutrophil engraftment for transplant recipients after transplantation was 20 days (range, 6–383 days) and 15 days (range, 1–378 days) for G-CSF− and G-CSF+ BM, respectively; 16 days (range, 9–101 days) and 13 days (range, 1–27 days) for G-CSF− and G-CSF+ PBSC related, respectively; and 20 days (range, 6–383 days) and 16 days (range, 10–154 days) for G-CSF− and G-CSF+ BM URD, respectively (P < .001). Duration of hospital stay was not affected by posttransplantation administration of G-CSF. Median duration of transplantation hospitalization was 30 days (range, 13–110 days) and 32 days (range, 12–185 days) for G-CSF− and G-CSF+ BM, respectively (P = .78); 23 days (range, 12–153 days) and 24 days (range, 3–158 days) for G-CSF− and G-CSF+ PBSCs, respectively (P = .4); and 31 days (range, 10–150 days) and 34 days (range, 13–248 days) for G-CSF− and G-CSF+ URD (P = .24), respectively.

Graft-versus-host disease

The cumulative incidences of grades II to IV acute GVHD in the G-CSF+ and G-CSF− cohorts were 26% versus 27%, respectively, among sibling BM recipients; 42% versus 35%, respectively, among sibling PBSC recipients; and 52% versus 50%, respectively, among URD BM recipients. In the multivariate analysis, administration of G-CSF within 7 days after transplantation did not significantly increase the risk for acute GVHD: sibling BM relative risk (RR) was 1.11 (95% confidence interval [CI], 0.86–1.42); sibling PBSC RR, 1.24 (95% CI, 0.95–1.62); and URD BM RR, 0.83 (95% CI, 0.65–1.04), after adjusting for significant covariates. Table 3 summarizes factors independently associated with increased risk for acute GVHD.

Table 2. Characteristics of patients by type of grafts

<table>
<thead>
<tr>
<th>Variable</th>
<th>BM</th>
<th>PBSC</th>
<th>URD</th>
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<tbody>
<tr>
<td>No. patients</td>
<td>1153</td>
<td>282</td>
<td>405</td>
</tr>
<tr>
<td>Age, y, median (range)</td>
<td>36 (&lt; 1-69)</td>
<td>34 (1-60)</td>
<td>33 (&lt; 1-59)</td>
</tr>
<tr>
<td>Males, no. (%)</td>
<td>617 (54)</td>
<td>156 (55)</td>
<td>244 (60)</td>
</tr>
<tr>
<td>KPS 80% to 100% at transplantation, no. (%)</td>
<td>916 (79)</td>
<td>233 (83)</td>
<td>311 (77)</td>
</tr>
<tr>
<td>Disease, no. (%)</td>
<td>AML 530 (46)</td>
<td>160 (57)</td>
<td>139 (34)</td>
</tr>
<tr>
<td>Disease stage, no. (%)</td>
<td>Early 889 (77)</td>
<td>202 (71)</td>
<td>256 (65)</td>
</tr>
<tr>
<td>Donor CMV positive, no. (%)</td>
<td>323 (28)</td>
<td>81 (29)</td>
<td>114 (29)</td>
</tr>
<tr>
<td>D/R sex match, no. (%)</td>
<td>F/M 257 (22)</td>
<td>67 (24)</td>
<td>76 (19)</td>
</tr>
<tr>
<td>Year of transplantation, no. (%)</td>
<td>1995-1996 556 (48)</td>
<td>120 (42)</td>
<td>130 (30)</td>
</tr>
<tr>
<td>No. centers</td>
<td>111</td>
<td>71</td>
<td>46</td>
</tr>
<tr>
<td>Median follow-up of survivors, mo</td>
<td>42 (3-87)</td>
<td>40 (3-77)</td>
<td>39 (3-82)</td>
</tr>
</tbody>
</table>

G-CSF indicates granulocyte colony stimulating factor; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; DR, donor-recipient; F, female; M, male; and TBI, total body irradiation.

*p < .05.
†p < .01.
transplantation did not significantly increase the risk for chronic GVHD. As shown in Table 4, sibling BM RR was 1.10 (95% CI, 0.86-1.39); sibling PBSC RR, 1.24 (95% CI, 0.94-1.63); and URD BM RR, 0.85 (95% CI, 0.63-1.15), after adjusting for significant covariates. Table 4 summarizes factors independently associated with increased risk for chronic GVHD.

Treat the cumulative incidences of TRM at 30 days, 100 days, and 1 year did not differ significantly by G-CSF administration across graft types. In multivariate analysis, administration of G-CSF within 7 days after transplantation did not significantly increase the risk for treatment-related mortality: RR was 1.26 (0.90-1.67) after sibling BM HCT; RR, 1.18 (0.86-1.63) after sibling PBSC HCT; and RR, 0.79 (0.60-1.03) after URD BM HCT, after adjusting for significant covariates.

The probabilities of leukemia-free and overall survival did not differ significantly between G-CSF and G-CSF− cohorts across graft types. This was confirmed in multivariate analysis where risks of mortality and treatment failure were similar in the G-CSF+ and G-CSF− cohorts across graft types. Administration of G-CSF within 7 days after transplantation did not significantly increase the risk for treatment failure (inverse of LFS): sibling BM RR was 1.05 (95% CI, 0.86-1.28); sibling PBSC RR, 1.08 (95% CI, 0.86-1.37); and URD BM RR, 0.93 (95% CI, 0.75-1.14), after adjusting for significant covariates. Similarly, in the multivariate analysis of overall survival, administration of G-CSF within 7 days after transplantation did not significantly increase the risk of mortality across the different types of grafts studied (Table 5): sibling BM RR was 1.11 (95% CI, 0.90-1.36); sibling PBSC RR, 1.07 (95% CI, 0.86-1.37); and URD BM RR, 0.83 (95% CI, 0.67-1.03), after adjusting for significant covariates.

**Discussion**

G-CSF has important immune modulatory effects that could affect the outcome of allogeneic transplantations, including (1) inducing a shift toward long-lasting type-2 immune reactivity10; (2) impairing production of IL-12 by Th2-inducing dendritic cells; (3) decreasing IL-12 receptor expression by IL-4- and IL-10-producing CD4+ cells; and (4) decreasing IFNγ and IL-4 production.11 These changes in the cytokine milieu might in turn affect susceptibility to
infection, GVHD, and graft-versus-leukemia effects, which could alter transplantation outcome. With administration of G-CSF to hasten posttransplantation neutrophil recovery, now a routine practice at many transplantation centers, prospective randomized trials assessing the nonhematopoietic effects of G-CSF are unlikely to be conducted. Therefore, this present study was done using a large registry database. The CIBMTR offers a unique opportunity to analyze high-quality data for a very large number of patients.

Our study found no risk or benefit of using G-CSF after transplantation in allotransplant recipients for myeloid leukemias. Noteworthy is the lack of improved early (days 30 and 100) TRM despite faster neutrophil recovery. Although this result derives from a very large cohort of patients, which should have had adequate statistical power to detect clinically meaningful differences, caution in interpretation is warranted since it was not a randomized trial. Since the conception of the present analysis, 2 other large studies have analyzed effects of posttransplantation G-CSF on transplantation outcomes. In a meta-analysis of 18 publications (9 prospective randomized trials, 2 retrospective cohort comparisons, 1 case-controlled analysis) comprising a total of 1198 patients, Ho et al examined the impact of posttransplantation G-CSF on GVHD. No increases in the incidence of either acute (RR, 1.08; P = .48) or chronic (RR, 1.02; P = .87) GVHD were detected. Posttransplantation G-CSF had no impact on TRM or on 100-day survival. In a second study, Ringdén et al analyzed the impact of G-CSF given within the first 14 days after transplantation on outcomes in 1789 allotransplant recipients. Compared with those who never received G-CSF, those who received G-CSF had more acute (RR, 1.33; P = .007) and chronic (RR, 1.29; P = .03) GVHD and an increase in TRM (RR, 0.59; P < .001). These effects were observed after BM but not PBSC transplantsations. Lower overall (RR, 0.59; P = .001) and disease-free (RR, 0.64; P = .003) survivals were also observed in BM recipients who received G-CSF. Of note, a study from the CIBMTR primarily intended to compare the outcomes of children and adolescents receiving either PBSC (n = 143) or BM (n = 630) grafts found that “growth factors” given within 7 days of HCT was a statistically significant covariate associated with higher treatment-related mortality, treatment failure, and overall mortality.

Our results are similar to those reported by Ho et al. but contradict those of Ringdén et al. Our study differs from the latter study in subject selection criteria and the cutoff day used to identify patients routinely receiving G-CSF after transplantation for hematopoietic recovery (as opposed to treatment for delayed recovery). Furthermore, our study was restricted to patient data derived from transplantation centers that routinely give G-CSF after transplantation to more than 80% of patients. This strategy was chosen to minimize selection biases that may be associated with giving G-CSF, particularly to minimize biases resulting from selection of high-risk patients to receive G-CSF to restore neutrophil counts in centers that would not give it otherwise. This bias could result in higher TRM and worse 100-day survival but does not explain the difference in GVHD risks. In the Ringdén et al study, a cutoff of 14 days was used to define subjects receiving G-CSF after transplantation. We repeated our analysis using the cutoffs of 10 and 14 days with no impact on our conclusions. In conclusion, we found no long-term risk or benefit of using G-CSF after transplantation in patients undergoing allogeneic HCT.

References

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