Nonmyeloablative Allogeneic Hematopoietic Cell Transplantation Following Fludarabine Plus 2 Gy TBI or ATG Plus 8 Gy TLI: A Phase II Randomized Study from the Belgian Hematological Society

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Abstract

Background. Allogeneic hematopoietic cell transplantation (allo-HCT) following nonmyeloablative conditioning is increasingly used as treatment for hematological malignancies in older patients or those with comorbidities. One of the most widely used nonmyeloablative conditioning associates fludarabine (90 mg/m² total dose) and 2 Gy total body irradiation (TBI) (Flu-TBI). This regimen can be safely performed in an outpatient setting but is associated with a relatively high incidence of graft-versus-host disease (GVHD). In an effort to prevent GVHD, the Stanford group have developed another nonmyeloablative conditioning that combines total lymphoid irradiation (TLI, 8 Gy total dose) with ATG (7.5 mg/kg Thymoglobulin® total dose) (TLI-ATG). As these 2 conditioning regimens have not been compared head to head, the Belgian Hematological Society (BHS)-transplantation committee initiated a phase II multicenter randomized study comparing nonmyeloablative allo-HCT with PBSC with either Flu-TBI (TBI arm) or TLI-ATG (TLI arm), and postgrafting immunosuppression with tacrolimus and mycophenolate mofetil. Here, we report the final analysis of the study.

Methods. Patients were randomized 1/1 between TBI or TLI arm. Main inclusion criteria consisted of hematological malignancies not rapidly progressing, age ≤ 75 years of age, and having a HLA-identical sibling donor or 10/10 HLA-matched related or unrelated donors who is fit to donate PBSC.

The primary endpoint was the 6-month incidence of grade II-IV acute GVHD.

Results. 107 patients were randomized in the TBI (n=55) or TLI (n=52) arms between January 2008 and March 2011 in one of the 9 participating centers. Thirteen patients (6 in the TBI and 7 in the TLI arm) were excluded from the analyses because they did not meet the inclusion criteria at the time of the start of the conditioning (disease relapse before the start of the conditioning (n=5), ineligible for further irradiation (n=3), donor refusal to give PBSC (n=2), HLA-mismatched donor (n=2), and poor performance status (PS) precluding transplantation (n=1)). One patient randomized in the TBI arm received the TLI conditioning (and was analyzed in intention to treat in the TBI arm). Thus, the analysis includes data from 94 patients randomized to the TBI (n=49) or TLI (n=45) arm. The 2 groups were well balanced. Median follow-up for surviving patients was 45 (range, 19-65) months. The 180-day cumulative incidences of grade II-IV acute GVHD were 12.2% versus 8.9% in TBI and TLI patients, respectively (P=0.5). Two-year cumulative incidences of moderate/severe chronic GVHD were 40.8% versus 17.8% in TBI and TLI patients, respectively (P=0.017). Four-year cumulative incidences of relapse/progression were 22% and 50% in TBI and TLI patients, respectively (P=0.017). The difference remained statistically significant in multivariate analysis (HR=2.3, P=0.02). Four-year cumulative incidences of nonrelapse mortality were 24% and 13% in TBI and TLI patients, respectively (P=0.5). Finally, 4-year overall (OS) and progression-free survivals (PFS) were 53% and 54%, respectively, in the TBI arm, versus 54% (P=0.9) and 37% (P=0.12), respectively, in the TLI arm.

Conclusions. In comparison to patients included in the TBI arm, patients included in the TLI arm had lower incidence of chronic GVHD, higher incidence of relapse and similar OS. The study was registered on ClinicalTrial.gov (NCT00603954).

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