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Graft-versus-Tumor Effects after Allogeneic Hematopoietic Cell Transplantation with Nonmyeloablative Conditioning.

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Abstract

We have used a nonmyeloablative conditioning regimen consisting of 2 Gy total body irradiation +/– fludarabine, 30 mg/m²/day x 3 days, to condition elderly or ill patients (pts) with hematological malignancies for allogeneic hematopoietic cell transplantation (HCT). This approach relies almost exclusively on graft-versus-tumor (GVT) effects for control of malignancy. Here, we analyzed GVT effects in 322 pts with hematological malignancies given grafts from HLA-matched related (n=192) or unrelated (n=130) donors. Grades I, II, III and IV acute GVHD were seen in 26 (8.1%), 141 (43.8%), 34 (10.6%) and 11 (3.4%) pts, respectively. Extensive chronic GVHD was seen in 181 (56.2%) pts and of these, 64 (19.9%) cases had de novo chronic GVHD. Putative GVT effects were evaluated using time-dependent Cox regression models. Of the 221 pts with measurable disease at HCT, 126 (57%) achieved complete (n=98) or partial (n=28) remissions. Multivariate analysis identified chemosensitivity for B-cell malignancies (p=.02), and tandem autologous/allogeneic HCT (p=.04) as pre-transplant factors associated with higher probabilities of achieving complete remissions (CR) after HCT. After adjusting for these factors, acute GVHD of any grade was not found to be associated with an increased probability of achieving CR. There was a trend for a higher probability of achieving CR in pts with chronic GVHD (p=.07). Progression/relapse was observed in 108 pts. Multivariate analysis identified that lower disease-risk (p=.0004), tandem autologous/allogeneic HCT (p=.02) and adapted Charlson comorbidity index (CCI) score at transplant < 3 (p=.002) resulted in significantly decreased risk of progression/relapse. After correcting for these factors, extensive chronic GVHD was associated with a decreased risk of progression/relapse (p=.006). Pts with grade 1 acute GVHD tended to have less progression/relapse (p=.07). Conversely, grade II–IV acute GVHD did not significantly affect the risk of progression/relapse. Nonrelapse mortality was observed in 70 pts. Multivariate analysis showed that lower disease-risk (p=. 001), tandem autologous/allogeneic HCT (p=.002) and CCI score at transplant < 3 (p<.0001) significantly decreased nonrelapse mortality. After adjusting for these variables, grade II (p=.04) and grade III–IV (p<.0001) acute GVHD increased nonrelapse mortality while extensive chronic GVHD did not. The 3-year probability of progression-free survival (PFS) was 38.5%. In multivariate analysis, lower disease-risk (p<.0001), tandem autologous/allogeneic HCT (p=.0008) and CCI score at transplant < 3 (p<.0001) resulted in significantly better PFS. After adjusting for theses variables, grade 1 acute GVHD (p=.02) and chronic extensive GVHD (p=.003) were both associated with significantly better PFS, while grade III–IV acute GVHD (p<.0001) was associated with decreased PFS. In summary, chronic GVHD in pts given nonmyeloablative conditioning was associated with substantial GVT effects which led to improved PFS. Conversely, any potential GVT benefits from grade II–IV acute GVHD were offset by higher nonrelapse mortality resulting in worse PFS. Efforts should be directed at reducing the risk of grade II–IV acute GVHD while allowing de novo chronic GVHD for best PFS after allogeneic HCT with nonmyeloablative conditioning.