larger numbers of patients might lead to different conclusions.

Finally, the authors found no relationship between chronic GVHD severity and relapse; this might be of interest but does not rule out that the graft-*versus*-leukemia effect is mainly restricted to NIH-defined chronic GVHD (and not to acute GVHD).[9]

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Stem cell transplants for myelodysplastic syndromes: refining the outcome predictions

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Myelodysplastic syndromes (MDS) are best regarded as a spectrum of diseases with distinct underlying biologies (as characterized by chromosomal abnormalities) and different prognoses. Disease characteristics and outcome of MDS are defined by two well-established classifications. Firstly, the FAB that segregates MDS by the degree of progression from relatively benign conditions with no excess of blasts (RA/RARS), excess blasts (RAEB), and the poor prognosis excess blasts in transformation to leukemia (RAEBt); secondly the IPSS score,[1] or its more recent modification the IPSS-R score,[2] which combines marrow blast cell counts with chromosomal abnormalities to identify low, standard, poor and very poor prognosis MDS. The very poor risk category is separated from the poor risk by the inclusion of monosomies 7 and 5.

These classifications are derived from the natural evolution of MDS in the setting of supportive care and non-curative therapy. The question, therefore, arises as to how applicable these scores are to MDS recipients of HSCT, which represents the only curative treatment for MDS. As age barriers fall away and transplant outcomes for older patients improve, more patients with MDS receive allogeneic SCT and it becomes increasingly important to define MDS risk categories to aid transplant selection.[3]

Outcome after HSCT for MDS is determined by patient characteristics and factors under the control of the transplant physician. Patient characteristics segregate into factors which impact on transplant-related mortality, such as age and general health (using an adapted Charleson score[4]), and those that impact the curative potential of the transplant. For this latter, transplanters have applied the FAB and IPSS score with or without inclusion of monosomy as a marker of very high relapse risk.

In this issue of the Journal, Oneda and colleages, reporting for the European Group for Blood and Marrow Transplantation (EBMT) on over 500 MDS patients undergoing matched sibling HSCT, explore the relevance of chromosomal abnormalities on predicting transplant outcome.[5] As predicted, the IPSS and FAB scores correlated broadly with outcome. They went on to show that presence or absence of karyotypic abnormalities had no impact on the outcome of the good risk FAB group (RA/RARS). In contrast, RAEB and RAEBt patients with poor risk karyotypes by IPSS criteria had an almost 2-fold increase in the risk of relapse and a correspondingly lower overall survival. Into this matrix they then factored the impact of chemotherapy given prior to transplant and the subsequent marrow blast percentage and remission status at transplant to compare four groups: RA/RARS *versus* untreated RAEB/RAEBt CMML *versus* non-RA/RARS treated and achieving first complete remission (CR1) *versus* non-RA/RARS not in CR1 at transplant. Best outcome (survival) was seen in the good risk RA/RARS group but treated patients in CR1 fared equally well (5-year survival 55%). In contrast, untreated

RAEB/RAEBt fared better than patients treated but not achieving CR1 (5-year OS 43% *vs*. 30%). Thus, these findings highlight the need to use multiple factors to best segregate transplant outcomes.

While this is an important study on a large patient population representing realistic outcomes for transplant teams in European countries, the findings remind us that more needs to be done before we can achieve a prognostic scoring system that has the power to separate subgroups into survival probabilities of, for example, over 90% and less than 10%. Such a system would permit not only the selection of the most favorable patients for transplant, but would eliminate the transplant option for patients where it represents therapeutic futility. Three recent reports on MDS from Italy,[6] Greece[7] and the United States[8] emphasize the strong negative impact of either the presence of monosomal chromosomal abnormalities, or the IPSS-R very poor risk MDS group, who carry chromosome monosomies. The EBMT population included only a small percentage of such patients and thus the impact of monosomy was not evaluable. To be fully inclusive, predictive scoring should incorporate factors that determine TRM as well as prognostic factors for relapse. Although age was factored in, the EBMT data lacked the modified Charleson score that could have refined prediction of outcome. The multicenter study from the Italian co-operative stem cell transplant group (GITMO)[6] in 519 MDS transplant recipients aged 17-72 years was able to combine disease characteristics (IPSS, monosomal karyotype and refractoriness to chemotherapy) with modified Charleson score and age, to identify a good risk group with a 70% survival, compared with the poorest risk group with zero survival (median survival <1 year). As older patients with MDS are increasingly offered SCT, the inclusion of age and comorbidity into outcome prediction will become more pressing. It will be important to see whether such a combined scoring system holds up and provides the same dichotomy of outcome in larger studies.

Finally, what can the transplanter do to optimize the transplant? Somewhat disappointingly, the EBMT study did not identify factors within the control of the transplanter that influenced outcome. Thus, neither the type of conditioning regimen, nor stem cell source or manipulation had a significant impact on outcome. It should be borne in mind that the interpretation of the impact of reduced intensity conditioning is complex and conditioning regimen intensity is easily confounded with patient age. While older patients receiving reduced conditioning may have the same outcome as younger patients receiving full conditioning, this similarity obscures the fact that the older patients have superior TRM but higher relapse rates. Sadly, the overall survivals for MDS patients did not exceed 50%. This all suggests that there are no easy fixes with stem cell source, type of conditioning or conventional post-transplant care that can make major improvements in transplant outcome. While we can expect TRM to continue to fall due to the effect of multiple factors [better antivirals, better graft-*versus*-host disease (GvHD) control, dissemination of expertise in transplant care] the relapse of MDS remains a huge challenge. Given the constraints on conditioning intensity, we must look to other means to reduce relapse. Current thinking favors boosting the graft-*versus*-leukemia (GvL) effect with innovative immunotherapy (immune enhancers such as lenalidomide, anti CTLA4, anti PDL1, adoptive transfer of tumor-reactive T cells and NK cells, vaccines),[9-11] strategies which enhance tumor antigenicity (e.g. azacytidine) and combining the GvL effect with small molecules that target some of the many karyotypic abnormalities that occur in this challenging syndrome.[12]

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