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CORRESPONDENCE

Progress in survival following three decades of allogeneic hematopoietic cell transplantation for myelodysplastic syndrome: A real-world registry study in Japan

To the Editor:

Allogeneic hematopoietic cell transplantation (HCT) can eradicate myelodysplastic syndrome (MDS) clones through high-dose chemoradiotherapy and the graft-versus-tumor effect,[1] and it remains the only potentially curative treatment modality for MDS. Although the improvement of transplant procedures, such as advanced supportive care and increased availability of unrelated donors, has resulted in progressive outcomes over time after allogeneic HCT,[2–4] the results for trends of transplant outcomes have been unclear for adult patients with MDS. Here, we investigated the trends in outcomes after allogeneic HCT for unselected adult MDS patients in Japan. Details for methods are provided in the supplemental methods (Data S1).

We identified 6257 adult patients with MDS who received their first allogeneic HCT between 1987 and 2020. Among them, 550, 1954, and 3753 patients were transplanted in 1987–2000, 2001–2010, and 2011–2020, respectively. Over the three time periods, there was a progressive increase in age at HCT, male recipients, poor karyotype, high-risk at HCT, diagnosis of HCT <6 months, unrelated donor, HLA mismatch, and graft-versus-host disease (GVHD) prophylaxis with methotrexate (Table S1).

The absolute annual numbers of HCT for age ≥60 years increased substantially over time, from 1 (1.9%) in 1997 to 245 (51.0%) in 2020 (Figure 1A). The absolute annual number of unrelated bone marrow transplantation (UBMT) has increased since 2004. More recently, the increase in unrelated cord blood transplantation (UCBT) was remarkable, from 1 (1.2%) in 1999 to 158 (32.9%) in 2020 (Figure 1B). As for conditioning intensity, both myeloablative conditioning (MAC) and reduced-intensity conditioning have increased over time, but MAC has been more commonly performed in all periods (Figure 1C).

The unadjusted probability of overall survival (OS) was not significant across the time periods (Figure 1D), whereas the unadjusted probability of disease-free survival (DFS) had significantly deteriorated between the time periods (Figure 1F). However, multivariate analyses showed that OS and DFS were significantly improved across the time periods (Table S2). The adjusted probabilities of OS and DFS improved over time (Figure 1E,G).

The unadjusted cumulative incidence of relapse deteriorated between the time periods (Figure 1H). In the multivariate analysis, the relapse rate was not significantly associated with the time periods. The adjusted cumulative incidence of relapse was not improved across the time periods (Figure 1I).

The unadjusted cumulative incidence of non-relapse mortality (NRM) had significantly improved between the time periods (Figure 1J). Multivariate analyses showed that NRM was significantly improved across the time periods (Table S2). The adjusted cumulative incidence of NRM improved over time (Figure 1K).

The most common cause of death was an infection in the first two time periods, but it was relapse or progression of MDS in the most recent period (Table S3). Thus, the proportion of deaths from relapse or progression of MDS increased in a stepwise fashion. Although the proportion of deaths from GVHD, pulmonary complication, organ failure, and hemorrhage decreased in the latter two time periods, the proportion of death from infection was not different across the three time periods.

Subgroup analyses showed that OS and DFS had significantly improved over time based on age, disease risk at HCT, donor type, and conditioning intensity, except that OS and DFS did not improve among patients aged 40–59 years and those with low risk at HCT (Figure S1, Table S4).

An important finding in our study was that the risk of relapse or progression of MDS after allogeneic HCT has gradually increased over time, and the proportion of death from relapse or progression of MDS has increased in a stepwise fashion. Such an increment of relapse or progression could have arisen because of the increased proportions over time of patients with advanced diseases, such as high-risk at HCT and poor karyotype. Therefore, to reduce the disease burden before allogeneic HCT, induction chemotherapy and hypomethylating agents have been tried in some patients with a higher disease burden. Indeed, the main change in clinical practice during the study period has been the introduction of azacytidine since 2011 in Japan. However, consistent with previous studies,[5,6] our study showed that the relapse rates and mortality did not improve in high-risk patients who received pre-transplant induction chemotherapy and hypomethylating agents compared to those who did not receive them, regardless of transplant year (Figure S2). This may reflect the selection bias that derives from the inclusion of patients with advanced diseases who received pre-transplant induction chemotherapy and hypomethylating agents. However, these pre-transplant treatments could be useful as a bridging therapy to allogeneic HCT that aims to avoid disease progression among patients with high disease burden. Furthermore, post-transplant maintenance strategies using several targeting agents might be beneficial, but their effects remain elusive for the further reduction

