Second chances – better than none

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In this issue of *Haematologica*, Yerushalmi and colleagues explore what happens to patients with acute myelogenous leukemia (AML) and myelodsyplastic syndromes (MDS) who relapse after a first allogeneic hematopoietic stem cell transplant (HSCT1) with the purpose of understanding the benefit of a second transplant (HSCT2) – the second chance.[1] When HSCT is performed in AML and MDS, relapse still remains the most common cause of failure even though the treatment is administered with the intent to achieve long-term survival free of graft-*versus*-host disease (GvHD). Of the 407 patients included in this single-center, retrospective study, 62 had HSCT2 (15%) and 345 did not. The 5-year overall survival rates were 25% (95% confidence interval [95% CI]: 14-36%) and 7% (95% CI: 4-10%) in the transplant and non-transplant groups, respectively (Figure 1). These results mirror the overall 10-15% long-term survival rate often quoted after post-transplant relapse and the long-term survival rates reported after HSCT2 by other single centers,[2,3] in cooperative groups,[4] or through meta-analysis.[5] In most of these studies, less than one third of patients reached HSCT2. In the study by Yerushalmi *et al.*, 28% of patients died in the first 2 months after relapse and could not be considered for HSCT2. Non-relapse mortality in this series was 26%, similar to that in many other studies,[2,3] and disease relapse was the main reason for lack of success after HSCT2.

The multivariable analysis conducted by Yerushalmi *et al.* demonstrated that female gender was the only factor associated with a better overall survival, whereas short remission after HSCT1, acute GvHD after HSCT1, HSCT2 from a haploidentical or matched unrelated donor, and relapse in earlier years of the study were associated with worse survival, suggesting that non-relapse mortality has improved with time. Why female recipients fare better in this situation is unclear and has not been noted in many other series. Others have found that chronic GvHD after the first transplant and a Hematopoietic Cell Transplant-specific Comorbidity Index of ≥2 are associated with inferior progression-free survival and overall survival after HSCT2.[3]

One of the important analyses in the paper by Yerushalmi *et al.* was a multivariable analysis of all relapsed patients, with HSCT2 entered as a time-dependent variable. This helped to eliminate some of the bias created by patients who progress or die early after relapse and never reach HSCT. In this analysis, female gender and having myeloablative conditioning during HSCT1 were associated with better outcomes, whereas relapse within 6 months after HSCT1, acute GvHD before relapse, relapse in earlier years, and not receiving a HSCT2 (P=0.01) were predictive of poorer overall survival. This may imply that those who are fit enough for ablative conditioning in HSCT1 will be more likely to meet performance status and co-morbidity criteria for HSCT2.

In almost all the series examining HSCT2 outcomes, the main cause of death is disease recurrence rather than GvHD or other non-relapse causes, and the majority of patients receive reduced intensity conditioning and most are in remission. Likewise, those who underwent HSCT2 in the study by Yerushalmi *et al.* tended to be younger than those who did not undergo HSCT2, but HSCT2 could be performed into the upper 70s, and median age at second transplant was 58 years. Most of the HSCT2 patients received GvHD prophylaxis with cyclosporine and methotrexate. Whether incorporation of post-transplant cyclophosphamide will influence the ability to perform second transplants favorably or unfavorably has not been examined, and most series reported to date have not included many patients undergoing haploidentical HSCT1. Most patients had HSCT1 when in first complete remission, but whether performed in first or subsequent remission did not influence outcomes after HSCT2. Minimal residual disease status was not available prior to either transplant. In univariate analysis, survival in those with active disease at the time of HSCT2 was no different from those in complete remission. This was not significant in multivariable analysis, and in most series, disease status at the time of HSCT2 is predictive of overall survival.[3]

In some centers, about half of second transplants are accomplished using the same donor as that for the first transplant[3] whereas in this series by Yerushalmi *et al.* only patients receiving grafts from different donors were considered to have undergone HSCT2. Most analyses have shown that whether the same or a different donor is used, overall survival is comparable.[5-7] Non-T-cell-depleted haplo-identical transplants have been used for HSCT2,

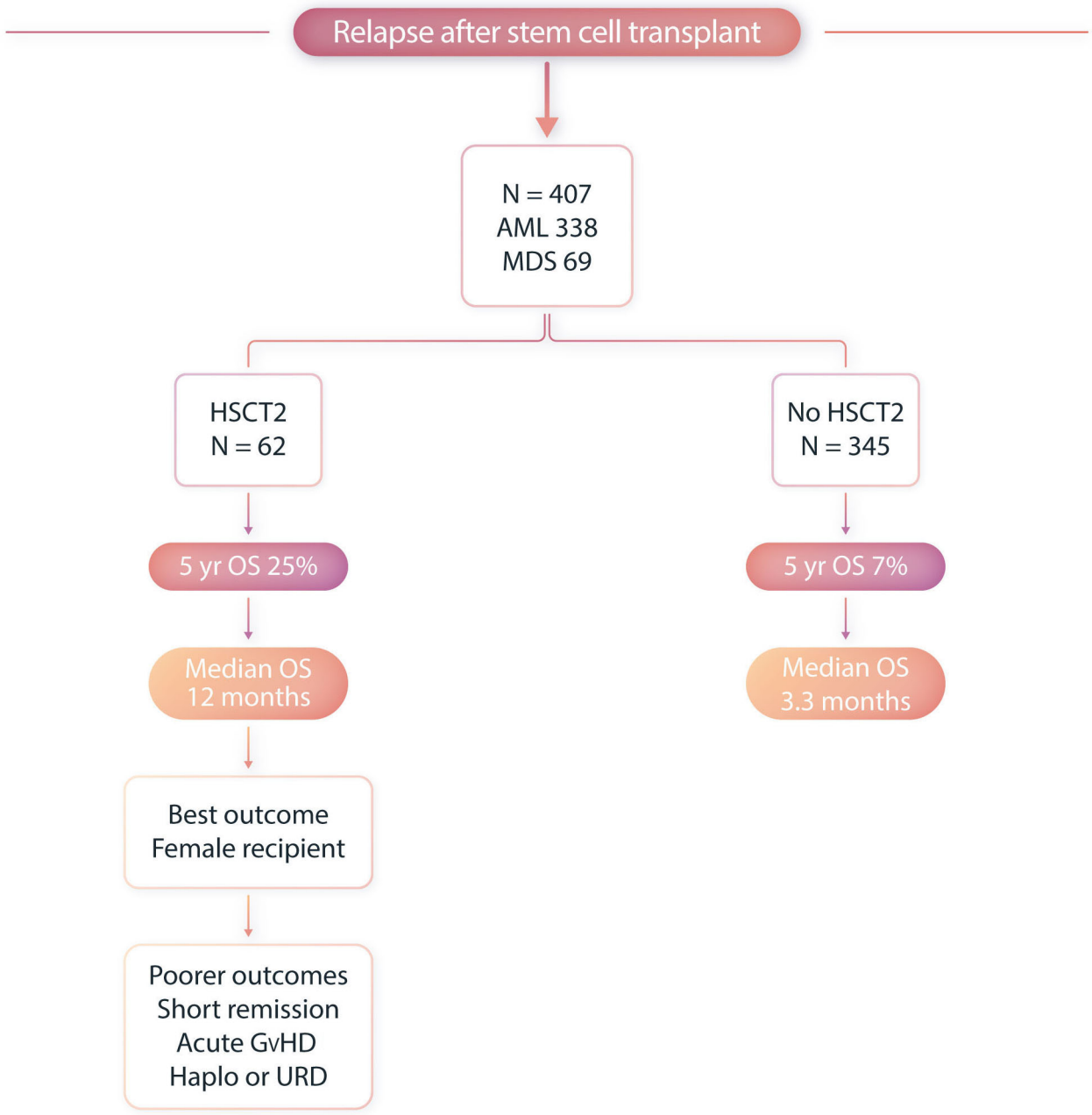

Figure 1. Disposition of the 407 patients who relapsed after hematopoietic stem cell transplant in the study by Yerushalmi *et al.*[1] AML: acute myelogenous leukemia; MDS: myelodysplastic syndrome; HSCT2: second hematopoietic stem cell transplant; OS: overall survival; GvHD: graft-*versus*-host disease; URD: unrelated donor.

but non-relapse mortality was higher, and overall survival was not better.[7]

Current management in the post-HSCT relapse setting is limited to supportive care, withdrawal of immune suppression, chemotherapy, hypomethylating agents,[8] targeted agents such as FLT3 or IDH2 inhibitors, donor leukocyte infusions, or HSCT2. More research is needed to find new effective therapies for post-HSCT relapse and to determine how available therapies can be best used. For example, can more effective bridging therapies that reduce disease burden pre-HSCT2 or more effective conditioning regimens for HSCT2 allow progress?[9] Also, hypomethylating agents alone or in combination with venetoclax are being used more commonly with or without donor lymphocyte infusions in patients who relapse after HSCT1. It will be interesting to study in the future how these regimens impact bridging to and results of HSCT2.[10]

The study by Yerushalmi *et al.* has the limitations of a single-center, retrospective analysis. Patients who relapsed after haploidentical transplants or cord blood transplants were not included in this series, and those who received a second transplant from the same donor (n=7) were not included in the HSCT2 group. Nevertheless, this work does add to our knowledge of what can be expected of second allografts and what variables are important to consider as decisions about treatment options are made with patients and families. While unlikely that a randomized study will ever be conducted to address post-relapse treatment options due to patients' heterogeneity, patient and physician preferences, and other logistical barriers, the emphasis must be on relapse prevention, early detection of relapse through measurable residual disease evaluation, and continued development of more effective immune therapies and targeted therapies which could have an impact in a post-transplant relapse setting. Anti-relapse strategies in those undergoing HSCT2 are also needed. The series presented here shows us that, to date, second transplants offer the best chance for survival, but better tolerated and more effective second chances are needed.

Disclosures

JL has sat on advisory boards for Blueprint Sciences, BMS, Servier, Pharmacosmos and Daiichi Sankyo, and participated in a Data Safety Monitoring Board for Syros.

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