Second Autologous Hematopoietic Stem Cell Transplant as Salvage Therapy for Relapsed Multiple Myeloma: A Global Treatment Option for Eligible Patients

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In this issue of *Acta Haematologica*, Muta et al. [1] report on the real-world experience of the Japanese population undergoing salvage autologous stem cell transplant (ASCT) for relapsed multiple myeloma (MM) using a large national registry database. Their findings confirm the results from many other similar retrospective and prospective studies conducted in Europe and the USA which demonstrate that salvage ASCT in relapsed MM is feasible [2, 3]. They demonstrate that patients enjoying a longer relapse-free survival after their first ASCT appear to do the best in terms of survival postsalvage ASCT. They also show that survival outcomes postsalvage ASCT have improved in the era of novel agents. Thus, this study provides further evidence to support the rationale of considering a second salvage ASCT as part of the therapeutic armamentarium of patients with relapsed MM who have enjoyed an adequate duration of disease control with their first ASCT. Finally, this study also confirms that the number of prior treatment regimens as well as chemosensitivity of the MM prior to salvage ASCT predicts survival outcomes. However, it is important to point out that this registry study did not include patients aged 70 years or more. Recent studies suggest that physiologically fit

patients with MM who are older than 70 years of age can also undergo ASCT and experience a similar efficacy as patients younger than 70 years of age [4].

MM remains the second most common hematological malignancy afflicting the human population. Though MM remains mostly incurable, the median survival of patients with MM has improved in the last 2 decades with the utilization of high-dose melphalan chemotherapy followed by autologous stem cell rescue (i.e., ASCT), as well as novel agents such as proteasome inhibitors and immunomodulators [5]. In the USA, MM is the most common indication for performing an ASCT. However, almost all patients with MM undergoing an ASCT will eventually experience disease relapse [6]. Thus, the need for salvage therapeutic options is critical in almost all patients with MM.

The study by Muta et al. [1] highlights the importance of salvage ASCT in relapsed MM and has several implications for clinical practice. First, it supports the need to reconsider individual institutional guidelines on initial stem cell collection goals for all eligible patients with MM. Collecting and storing enough stem cells at the time of initial stem cell mobilization for use at a later time point, such as disease relapse, can prove convenient as well as

cost-effective for patients with relapsed MM. Second, with the advent of triplet, novel agent-based therapies being used as salvage options for patients with relapsed myeloma, the monthly cost of treating patients with relapsed MM has skyrocketed. In fact, some regimens given over an entire year are far more expensive than conventional ASCT using high-dose melphalan. Finally, if appropriately selected, patients with relapsed MM are likely to enjoy more than 1–2 years of disease control after salvage ASCT. Most of the time, this duration of disease control with salvage ASCT can be far superior to that experienced by patients with relapsed MM being treated with novel agent regimens.

Unanswered questions that remain are the appropriate conditioning regimen to be used for salvage ASCT. This registry database lacked information on the dose of melphalan used. However, it is only logical to question whether alternate forms of conditioning chemotherapy would be more appropriate, especially after a history of disease relapse to prior high-dose melphalan. Ongoing clinical trials adding novel agents such as proteasome inhibitors

and monoclonal antibodies to high-dose melphalan are being investigated and could eventually change the conditioning chemotherapy regimen used for salvage ASCT. Recent clinical trial data suggest that upfront tandem ASCT may be the optimal treatment for high-risk disease. However, it remains unclear whether salvage ASCT would confer the same amount of clinical benefit in MM patients relapsing after having undergone a tandem ASCT. Finally, a future intriguing question will be whether performing salvage ASCT is appropriate with the availability of novel cell-based therapies such as chimeric antigen receptor-T cell (CAR-T) technology. Nevertheless, for now Muta et al. [1] remind us of the role of a second ASCT as a global salvage treatment option for eligible patients with relapsed MM.

Disclosure Statement

The authors declare no conflicts of interest.

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