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## **Autologous Transplantation in elderly multiple myeloma patients: is the procedure cost-effective?**

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The survival of multiple myeloma (MM) patients significantly increased in the last decades, due to the introduction of novel agents (immunomodulatory agents [IMiDs] and proteasome inhibitors [PIs]). This improvement was recently seen also in patients older than 65 years of age. This was probably related to better supportive measures that translated into a decrease in early mortality rate.<sup>1</sup> Patients older than 65 years of age are generally considered ineligible for high-dose chemotherapy and autologous transplant (ASCT), especially in Europe. For younger patients, ASCT is currently the standard of care. ASCT improved overall survival (OS) as compared with chemotherapy,<sup>2-4</sup> and recently it showed to be superior also to chemotherapy plus IMiDs.<sup>5</sup> In the US, Medicare covers the costs associated with ASCT for patients up to 78 years of age, with a consequent rise in the utilization of ASCT in the elderly population. Results on the efficacy of ASCT in patients older than 65 are not univocal. There is only one trial that compared reduced-intensity ASCT vs chemotherapy plus IMiDs. The trial showed an improved OS for patients randomized to chemotherapy plus IMiDs;<sup>6</sup> nevertheless, patients randomized to ASCT did not receive any novel agent upfront, and this could have at least in part biased the results. Results of a phase II trial evaluating novel agents plus reduced intensity ASCT in the elderly suggested a greater efficacy of ASCT even in this population.<sup>7</sup> A recent retrospective analysis including patients treated in the last 15 years, showed an OS advantage also in patients older than 65 years who received ASCT in comparison with patients who did not.<sup>1</sup> With all the limitations, there are still signs of improvement with ASCT in elderly patients.

The increased utilization of novel agents in MM treatment augmented the cost of therapy over time,<sup>8</sup> as did the administration of high-dose therapy and transplant.<sup>9</sup> The cost of treatments raises reasonable concerns. Health care systems aim to maximize the outcome while working with a tight budget. Thus, physicians should keep into account not only the efficacy but also the cost-effectiveness of different treatment options when selecting therapy.

In this issue of *Biology of Blood and Bone Marrow Transplant*, Shah et al. evaluated the cost effectiveness of ASCT in patients over the age of 65 using a large data set of US national data.

They included 270 patients who underwent ASCT and 270 matched patients who did not. First, the population of patients included represents a good sample of elderly patients eligible for ASCT: the median age was 68 years (with less than 10% of patients older than 75 years) and two thirds of them had no comorbidities. Second, in this population of patients, the median OS in patients who underwent ASCT was 58 months, significantly longer than the value reported in patients who did not (37 months), thus suggesting that elderly patients who are fit and able to undergo ASCT benefit from this treatment. Third, the authors calculated an average incremental cost-effectiveness ratio of less than \$100,000 per life-year gained (\$72,852 per life-year gained) and showed that ASCT in eligible patients older than 65 years is cost-effective 90% of the times.

The current article strengthens the idea that ASCT in eligible patients older than 65 years is an effective option. Patients undergoing ASCT lived approximately 1.37 years longer than patients who received a different treatment. The survival rate reported is comparable to previously published studies enrolling younger patients.<sup>2-4</sup> Nevertheless, recent studies with ASCT in patients up to 65 years of age do report longer survival times<sup>5</sup>, but this difference could partly be explained by the wider access to novel agents in more recent years (the timeframe analyzed in this study was 2000-2007). The authors evaluated a large set of "real world" national data, providing results coming from the real life context that confirm the promising results coming from clinical trials in this setting. This is of course a key consideration, even if this analysis needs to be re-evaluated outside the US, given the different availability and cost of drugs worldwide. In the present study the authors selected patients who received ASCT, thus excluding from the analysis those patients who were

considered eligible for ASCT at diagnosis, but that did not receive it for early progression or for toxicity experienced during induction. This could be a limitation of the study, related to its retrospective nature. Of note, it is necessary to understand that these results do not apply to all elderly patients, but only to those eligible for the procedure. Patients undergoing ASCT in the Medicare Database had a median age of 68 years (2/3 of them younger than 70 years), and most of them had no comorbidities. Other reports showed that induction treatments and ASCT in the elderly population are more feasible in patients younger than 70 years.<sup>7</sup> Fit patients with no comorbidities are those who can tolerate the procedure better, with less adverse events and a better safety/efficacy profile. Less adverse events translate into a better quality of life and lower costs for the Health Systems. The correct identification of patients who may benefit from a specific treatment is the first step to maximize the cost-efficacy ratio associated with therapy. In the subset of elderly patients eligible for ASCT (the authors appropriately matched patients according to several variables including age and comorbidities), ASCT was cost-effective 90% of the times.

A second limitation of the present analysis is that the cost of oral drugs (IMiDs) was not included. In present years, the use and the availability of novel agents has considerably increased. Several combinations including second- and third-generation, high-priced IMiDs and PIs are currently under investigation in the newly diagnosed and relapsed settings, and these agents are used both in strategies that incorporate ASCT or not. In terms of efficacy, a number of combinations can challenge the role of ASCT. A recent review suggested that many new treatments for hematologic malignancies including MM are also cost-effective.<sup>10</sup> The impact of transplantation on outcome and its cost-effectiveness need to be evaluated in the context of the currently approved treatments. More efforts are required to compare and clarify the cost-effectiveness of current available treatments to encourage cost-conscious responsible choices that could improve health outcome and save money.

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