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Short review

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# Should young patients with high-risk multiple myeloma be offered allogeneic transplants? A vote in favour

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The prognosis of patients with multiple myeloma has improved markedly over the last two decades. Despite that, allogeneic hematopoietic stem cell transplantation remains the only treatment option with curative potential. Therefore it should be considered for younger patients, especially those with high-risk disease as defined based on revised international scoring system. A decision to use transplantation, as well as the choice of conditioning regimen should be personalized, taking into account a particular center's experience.

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**Key words:** multiple myeloma, allogeneic hematopoietic cell transplantation, conditioning

The prognosis of patients with multiple myeloma (MM) has improved markedly over the last two decades [1]. This is due to the introduction of immunomodulatory drugs such as thalidomide, lenalidomide, pomalidomide and proteasome inhibitors: bortezomib, carfilzomib. Administration of these drugs at the induction stage allows for obtaining a large percentage of total and partial remissions. On the other hand, the depth of response translates into a longer time of progression-free survival (PFS) and overall survival (OS) [1]. This effect can be enhanced by applying high-dose therapy, usually melphalan at a total dose of 200 mg/m$^2$ of body surface area, which requires support with autologous hematopoietic cell transplantation (autoHCT). AutoHCT remains the standard of management in younger patients, conventionally under 65 years of age [2]. The results of some clinical trials indicate that dual autoHCT may contribute to a further increase in OS time, although this issue remains controversial [3]. The results of meta-analysis of three clinical trials also indicate that maintenance with lenalidomide has a beneficial effect on survival [4].

Despite significant progress in pharmacotherapy, MM is still considered an untreatable disease. Following initial response, progression almost inevitably occurs, and the effectiveness of subsequent treatment lines is decreasing. The prognosis of patients with PFS and OS can be estimated using a Revised International Scoring System (R-ISS) [5]. It takes into account the concentration of β-2-microglobulin and serum activity of lactate dehydrogenase, as well as karyotype features of neoplastic cells. The median PFS for patients with R-ISS I, II and III values was shown to be 66, 42 and 29 months, respectively [5]. In turn the median OS in case of R-ISS = III is 42 months [5]. In a more recent analysis by Kastritis et al. this median was only 27 months [6]. While these survival times may be considered satisfactory for elderly patients, they are difficult to accept for younger ones. Although MM is a disease typical of older age, it is also diagnosed in persons being 30 or even 20 year old. Jurczyszyn et al. published an analysis covering 173 patients aged 21–40 years and 916 patients aged 41–60 years [7]. The OS probability after 10 years was 56% and 39%, respectively. However, it was significantly worse in patients with ISS = II or III, without differences depending on the age group. Moreover, it has been demonstrated that in younger patients unfavorable cytogenetic changes are more frequent [7]. The above data indicate the need to look for a more radical treatment strategy for younger patients with MM, especially if they have risk factors associated with shorter expected time of PFS and OS.

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The only therapeutic method giving a chance to cure MM patients is allogeneic hematopoietic cell transplantation (alloHCT). It offers a possibility of applying myeloablative doses of chemotherapy or irradiation, called conditioning, without the risk of cancer cell re-transplantation. The efficacy of alloHCT is also a result of a graft versus myeloma reaction, which is caused by alloreactive T lymphocytes present in the transplant material. They can eliminate residual myeloma cells in the recipient's body, contributing to the cure. Nowadays it is possible to identify a potential donor for almost every patient. These may be HLA-matched sibling, matched unrelated donor, but also a family donor matching with only one HLA haplotype.

Unfortunately, alloHCT procedure is associated with a very high risk of complications, including life-threatening ones. This applies to the toxicity of conditioning, infectious complications resulting from long immunosuppression, as well as graft versus host disease, which is an expression of alloreactivity of donor lymphocytes against recipient's healthy cells. In historical analyses, the risk of transplant-related mortality (TRM) in myeloablative-conditioned transplants reached 40% [8]. It should be noted, however, that these were patients at late stages of the disease, in which many therapy lines were used earlier, with numerous coexisting diseases. At the end of the 20th century, alternative preparative regimens of reduced intensity were developed. The main purpose of conditioning was to enable engraftment, assuming that the graft versus myeloma reaction would be sufficient to obtain a cure. TRM was limited considerably, the risk of progression was, however, significantly higher in comparison with myeloablative-conditioned transplants [8]. The next step were tandem transplantations, in which in the first stage autoHCT was performed in order to reduce the tumor mass as much as possible, and then alloHCT with reduced-intensity conditioning. A number of prospective clinical trials have been conducted comparing this strategy with the tandem autoHCT one. Two studies showed an advantage of auto-alloHCT over auto-autoHCT in relation to PFS and OS, while in the remaining five such a relationship was not found [9]. The meta-analysis of these studies did not lead to the formulation of unambiguous conclusions [9].

Taking into account historical experiences indicating excessive toxicity of traditional myeloablative protocols and insufficient effectiveness of alloHCT with reduced conditioning intensity, it seems advisable to look for a "third route", i.e. preparation with myeloablative potential, which, however, would be characterized by better tolerance. At Maria Skłodowska-Curie Cancer Center and Institute of Oncology, Branch in Gliwice, a new protocol has been developed, which may satisfy these conditions. It is based on a tandem strategy: auto-allo-HCT. In the autoHCT procedure, melphalan is used at a dose of 200 mg/m$^2$ of the body surface area. After about three months, alloHCT is performed with bendamustine conditioning in combination with total marrow irradiation (TMI). The TMI is performed with helical tomotherapy using three fractions of 4 Gy each, i.e. a total of 12 Gy. This is a myeloablative dose, but focused on the skeleton, i.e. the natural location of MM cells. On the other hand, the dose for organs which are supposed to be free from disease, i.e. lungs, heart, liver, gastrointestinal tract is very limited. Initial experience of 14 patients aged 28–55 years treated in this way points to good tolerance and lack of TRM, with a PFS probability of 78% after 2 years (unpublished data).

To sum up, alloHCT remains the only option giving a chance to cure MM patients. In younger patients, indications should be determined on individual basis, taking into account the risk factors of failure of conventional pharmacotherapy, but also the patient's attitudes and experience of the centre. It is advisable to search for forms of conditioning of reduced toxicity with preserved myeloablative potential. In the future, new forms of cellular immunotherapy, e.g. the use of T lymphocytes with a chimeric antigen receptor, may be a safer and potentially more effective alternative [10].

**Conflict of interest**: none declared

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