sion. The levels of competence and their descriptions were revised to meet with the standard EU formulations. The diagnostic parts were modified, where relevant, to assess competence in interpretation of diagnostic tests rather than hands-on ability to perform them. With increasing demands for accreditation in particular within the laboratory specialties this is a logical development, but it remains to be seen if young hematologists would score better in the new version of the European Hematology Curriculum. The new CV Passport, revised according to the European Hematology Curriculum, is internet-based and includes tags to selected educational material for each section and individualized interactive features which makes it an ideal tool for self-assessment by hematologists in training.

It is difficult to underestimate the importance of the European Hematology Curriculum in the context of an integrated Europe. Now there is professional consensus where the scope, content and minimum competences of our medical specialty are concerned. Meanwhile, Europe is slashing its borders to allow for free movement of its citizens. This development may or may not deliver on its promise of professional mobility, employment opportunities and, finally, greater prosperity and equity for all. But it will definitively affect the geographical scope of training medical specialists. To have already come so far as to agree upon a European Hematology Curriculum is one thing. Another is to acquire knowledge about the educational realities that exist in the different countries in order to face the challenges that Europe is posing. To this end it is important to regularly perform the Competence Survey and to act upon its results.

Testing the relevance of the European Curriculum version 2.0: a prospective European survey

A prospective continuous survey would be the ideal next step in assessing the present and future impact of the European Curriculum on hematology training in Europe. If implemented as a self-assessment tool for hematology trainees at all stages of training, competence information could be gathered at any time from the beginning of training until up to two years following completion of training.

The competence data registered in this survey would, first and foremost, enable trainees to monitor their own progress and ensure they have covered all the diverse areas which hematology encompasses. The survey would also enable the generation of national or regional reports, providing important information regarding the patterns of hematology competence in various regions of Europe. This will enable national societies to monitor how learning objectives are met over time and change training programs in response to the shortfalls that may have been identified.

This prospective survey could be an important tool to ensure and increase the quality of professional competence in this specialty. It may provide trainees with a tool for professional excellence and mobility. In addition, national societies will be able to assess the efficacy of their training programs and adapt them if necessary, thereby promoting harmonization of hematology training in Europe.

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References

1. Ossenkoppele G, Evans-Jones G, Jaeger U, Hellström-Lindberg E; Curriculum Update Working Group. Towards a joint definition of European hematology. Haematologica. 2012;97(5):636-7.
2. Duyvené de Wit T, Hellström-Lindberg E, Jäger U, Evans-Jones G, Smand C. H-Net, the European Network for Harmonization of Training in Hematology, and its policy. Haematologica. 2012;97(12): 1776-8.
3. Strivens J, Hellström-Lindberg E, Bjerrum OW, Toh CH. A European strategy for targeted education in hematology. Haematologica. 2013;98(7):1000-2.

Treatment of autologous stem cell transplant-eligible multiple myeloma patients: ten questions and answers

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Autologous stem cell transplantation is currently considered the standard of care for multiple myeloma in young patients with adequate organ function, based on the results of trials conducted in the era prior to the advent of novel agents. While these trials demonstrated the superiority of high-dose therapy with stem cell support over conventional chemotherapy, relapse remained an issue for the majority of patients. With the introduction of the novel agents, a dramatic change in treatment strategies in the transplant setting has taken place. These agents are now incorporated prior to and following the transplant procedure, and have resulted in improvements in outcome. Importantly, improvements have also been seen in patients with high-risk cytogenet-

Table 1. Induction regimens.

Induction regimen	Response post-induction (%)		Response post-ASCT (%)	
	CR	≥ VGPR	CR	≥ VGPR
TAD *vs.* VAD[11]	3 / 2	37* / 18	14 / 12	66* / 54
CTD *vs.* CVAD[13]	13* / 8	43‡ / 27	50* / 37	74‡ / 62
Bortezomib/dex *vs.* VAD[12]	6* / 1	38* / 15	16* / 9	54* / 37
PAD *vs.* VAD[14]	7* / 2	42* / 14	21* / 9	62* / 36*
VTD *vs.* TD[6]	19* / 5	62* / 28	42* / 30	82* / 64
vTD *vs.* VD[16]	13 / 12	49* / 36	29 / 31	74* / 58
VTD *vs.* TD *vs.* VBMCP/VBAD+V[18]	35* / 14 / 21	60‡ / 29 / 36	46† / 24 / 38	n/a / n/a / n/a

ASCT: autologous stem-cell transplantation; CR: complete response; VGPR: very good partial response. **P value statistically significant;* ‡*Information regarding* P*-values not available;* †*P value VTD* versus *TD statistically significant.*

ics and renal impairment. In the era of novel agents, the role of transplant itself is being questioned and trials are ongoing to establish whether transplant can be delayed until after relapse in some patients. The current ongoing studies are aimed towards improving the different steps of the procedure with the aim of further improving efficacy and tolerability. This review addresses a number of questions surrounding the different steps of the transplant procedure and summarizes the available research evidence as a basis for decision making.

1. Is high-dose therapy plus autologous stem cell transplantation superior to conventional chemotherapy?

The concept of high-dose therapy (HDT) plus autologous stem cell transplantation (ASCT) was developed in the 1980s. The objective of ASCT was to support high-dose therapy (HDT) in order to reduce the duration and toxicity of severe myelosuppression. The Intergroupe Francophone du Myelome (IFM) was the first to conduct a randomized trial showing the superiority of HDT/ASCT over conventional chemotherapy in patients under 65 years of age regarding response rate, event-free survival (EFS) and overall survival (OS).[1] These findings were confirmed seven years later in a larger study conducted by the UK Medical Research Council (MRC Myeloma VII trial).[2] Following these results, HDT/ASCT became the standard of care in patients without severe comorbidities and under 65 years of age.

Overall, 7 randomized studies have compared ASCT/HDT to conventional chemotherapy.[3] While EFS was superior with HDT/ASCT in 5 of 7 trials, OS was significantly prolonged in only 3 trials. These results were confirmed by a meta-analysis that showed a significant benefit for HDT/ASCT in terms of EFS but no benefit in terms of OS.[4] This was partly explained by the impact of ASCT at relapse in patients initially treated with conventional chemotherapy. Therefore, although the majority of myeloma experts recommend HDT/ASCT as part of initial therapy, some experts consider that delaying ASCT until relapse remains a valuable approach.

Importantly, the use of HDT/ASCT was the major cause of OS improvement observed in younger patients before the introduction of novel agents, such as immunomodulatory drugs (IMIDs) and proteasome inhibitors.[5] However, despite the demonstrated efficacy of the procedure, relapses ultimately occurred in the vast majority of patients and long remissions (and possible cures) remained rare. The introduction of several new agents (thalidomide, lenalidomide and bortezomib) has substantially changed treatment strategies in the transplant setting. The addition of novel agents before and/or after HDT/ASCT has dramatically increased the post-ASCT complete response (CR) rate and the CR plus very good partial response (VGPR) rate.[6,7] Maybe more importantly, the level of CR has been up-graded with the achievement of stringent CR (s-CR) with a normal κ/λ ratio (serum free light chain assessment),[8] of immunophenotypic CR (with multiparameter flow cytometry)[9] and even molecular CR.[10] Achievement of immunophenotypic or molecular CR has been associated with longer progression-free survival (PFS) and might become a new objective of modern treatments with novel agents plus HDT/ASCT.

2. What is the best induction treatment prior to autologous stem-cell transplantation?

The objectives of including induction treatment prior to HDT/ASCT are to reduce the tumor burden in order to increase the post HDT/ASCT CR rate and to decrease the plasma cell marrow infiltration to improve the quality of the graft.

The ideal induction treatment should be well tolerated and should spare normal hematopoietic precursors. Prior to the introduction of novel agents, alkylating agents were avoided due to their hematopoietic toxicity and the standard induction regimen was dexamethasone-based, either high-dose dexamethasone alone, or a combination of dexamethasone with non-alkylating cytotoxic agents, such as doxorubicin and vincristine in the so-called VAD regimen.[3]

Over recent years, a number of randomized studies have demonstrated the superiority of induction regimens containing one or two novel agents (thalidomide or bortezomib) compared to VAD-based regimens[11-14] (Table 1). With these new regimens, pre-ASCT response rates were superior, with higher CR rates, as well as higher CR plus near-complete response (n-CR) or VGPR rates. More importantly, this better efficacy translated into higher CR or CR plus n-CR or VGPR rates post transplantation. Therefore, VAD is no longer considered the standard induction treatment.[7,15]

Three randomized studies have compared a two-drug induction (TD: thalidomide-dexamethasone or VD: bortezomib-dexamethasone) with a three-drug regimen (VTD: bortezomib, thalidomide, dexamethasone).[6,16,17] In the 3 studies, VTD was significantly superior to the two-drug regimen and is now considered a standard induction regimen (Table 1), although in the study by Rosiñol *et al.*, VTD was not able to overcome the poor prognosis impact of high-risk cytogenetics. There is no evidence that 4-drug regimens are superior and they may be more toxic.[19,20]

The better response rate observed with new regimens is

related to a better efficacy across all prognostic subgroups, including ISS 3 and poor-risk cytogenetics.[6,12] There is currently no direct evidence that the higher CR plus n-CR rate achieved with these new regimens translates into a longer PFS since in all of these studies, there were different post-ASCT treatments. However, there is an indirect argument in favor of the prognostic impact of a better induction treatment: the IFM group has shown that achieving at least a higher VGPR rate after induction is associated with a longer PFS.[21] New induction regimens with lenalidomide and carfilzomib are currently under evaluation.

3. What is the optimal conditioning regimen prior to autologous stem cell transplantation?

The first HDT regimen was the combination of intravenous (i.v.) high-dose melphalan (HDM) (140 mg/m^2) plus total body irradiation (TBI). In a randomized trial conducted by the IFM, high-dose melphalan alone at a dose of 200 mg/m^2 was shown to be superior to HDM plus TBI.[22] Thus far, HDM 200 mg/m^2 is, therefore, the most widely used HDT regimen. However, to improve the efficacy of the HDT and ASCT results, several procedures have been tested. Different groups have explored the use of combination HDT conditioning regimens using agents in addition to or replacing HDM.[23,24] Recently, the Spanish group tested a combination of oral busulfan combined with HDM.[25] Unfortunately, despite the fact that median PFS was significantly longer with oral busulfan combined with HDM, this regimen was associated with higher toxicity due to an increase in the incidence of veno-occlusive disease. Subsequently, oral busulfan was substituted by i.v. busulfan,[26] which proved to be effective in reducing the incidence of severe toxicities.[27] However, i.v. busulfan combined with HDM was not superior to HDM alone and median PFS was comparable between both groups.[26] Thus, one can conclude that, for the time being, none of these approaches proved to be superior to HDM 200 mg/m^2.

The use of bortezomib in conjunction with high-dose melphalan proved to be well-tolerated, with non-randomized data suggesting improved efficacy.[28,29] However, until randomized results are available, HDM 200 mg/m^2 should remain the standard HDT prior to ASCT.

4. What is the best stem cell mobilization procedure prior to autologous stem cell transplantation

Hematopoietic stem cell (HSC) mobilization from bone marrow to peripheral blood is an essential part of ASCT programs to increase the number of HSC cells in the peripheral blood. Current mobilization strategies vary between centers and some patients are unable to mobilize sufficient numbers of peripheral blood stem cells (PBSC).[1] Mobilization with granulocyte colony-stimulating factors (G-CSF) is the most commonly used steady-state mobilization strategy.[30] Currently, the G-CSF cytokines filgrastim and lenograstim are approved for the mobilization of autologous HSC. The recommended schedules are filgrastim 10 μg/kg/day for 4-6 consecutive days and apheresis to be performed on Days 5 or 6. Lenograstim is used at 10 μg/kg/day for 4-6 days and apheresis are to be performed between Days 5 and 7. Mobilization with cytokines alone is well tolerated but their use can be limited by suboptimal PBSC yields.[31] Adding chemotherapeutic agent(s) to cytokines may increase PBSC yields (so called "chemomobilization" procedure) and can potentially decrease the tumor burden. However, the time required to collect PBSCs is prolonged and adequate collection becomes less predictable. Also, the incidence and severity of side-effects with chemotherapy plus G-CSF is increased compared with G-CSF alone. The widely accepted filgrastim and lenograstim dose for PBSC mobilization after myelosuppressive chemotherapy is 5 μg/kg/day each, starting within 1-5 days after completion of chemotherapy and continuing until the last apheresis. The most commonly used chemotherapy-based mobilization in myeloma includes high-dose cyclophosphamide (usual doses are in the range of 2-4 g/m^2).[32] Current mobilization strategies can be optimized by different approaches: i) re-mobilization with steady-state approach; ii) change in chosen chemo-mobilization approach; or iii) addition of new mobilization agents such as plerixafor.[33] Plerixafor is a chemokine-receptor 4 (CXCR4) antagonist that disrupts the interaction between the stromal-derived factor 1 (SDF-1) and CXCR4, thereby enhancing the stem cell mobilization effect of G-CSF. Plerixafor has been approved for use in combination with G-CSF for autologous HSC mobilization in myeloma and lymphoma patients. The recommended dose is 240 μg/kg body weight/day 6-11 h prior to apheresis initiation following four days of G-CSF pretreatment.[31]

Table 2. Consolidation studies.

Study	N.	Outcome
Phase III		3-year PFS
VTD *vs.*	160	62%
TD[35]	161	46%; *P*=0.042
Phase III		progression-free survival
Bortezomib *vs.*	187	27 months
N. treatment[37]	183	20 months; *P*=0.05
Retrospective study		relapse rate
VTd *vs.*	121	21%
N. treatment[36]	96	45%; *P*=0.001

5. What is the impact of consolidation therapy after autologous stem cell transplantation?

The use of short-term consolidation therapy after HDT and ASCT aims to improve disease response through the induction of a deeper response. It is widely accepted that consolidation therapy should rely on a highly efficient combination of drugs with limited toxicity, and that it should be administered for a limited period of time. Experiences testing consolidation therapy in myeloma remain scarce given that they started in the era of novel therapies. Initial results suggest that novel agents after ASCT may further increase the rate of high-quality responses and improve both PFS and OS.[34] In patients with a good response after ASCT, consolidation therapy has been found not only to increase the complete response (CR) rate but also to yield molecular remissions, which are associated with longer PFS.[10] Only a few large studies investigating novel agent-based consolidation therapy are available so far (Table 2). The Italian myeloma study group reported results from a randomized, phase III study

Table 3. Lenalidomide maintenance trials.

Study	Median follow up	N.	Treatment	Outcome	
				PFS	4-year OS
IFM 2005-02[41]	45 months	307	Lenalidomide	41 months	73%
		307	Placebo	23 months	75%
				P<0.001	*P*=ns
				TTP	OS
CALGB 100104[42]	48 months	231	Lenalidomide	50 months	Not reached
		229	Placebo	27 months	n=73
				P<0.001	*P*=0.008

PFS: progression-free survival; OS: overall survival; TTP: time to progression.

Table 4. Bortezomib maintenance trials.

Study details	Median follow up	N.	Treatment	Outcome	
				PFS	OS
HOVON 65 MM / GMMG-HD4[14]	41 months	413	PAD/HDM/Bortezomib	35 m	Median not reached
		414	VAD/HDM/Thal	28m	HR=0.77
				P<0.001	(0.60-1.00) *P*=0.049
PETHEMA / GEM[17]	34.9 months	89	VT	Significant PFS	OS not significantly
		87	Thal	benefit for VT	diffferent
		90	Interferon-α2b	*P*<0.0009	between arms

PFS: progression-free survival; OS: overall survival.

that assessed the efficacy of bortezomib, thalidomide, and dexamethasone (VTD) *versus* thalidomide and dexamethasone (TD) as induction therapy before and as consolidation therapy after double ASCT for newly diagnosed myeloma patients.[6] In this randomized study, superior complete/near-complete response (CR/nCR) rates and extended PFS were demonstrated with VTD *versus* TD as induction therapy before, and two cycles of consolidation after, double ASCT. A recent *per*-protocol analysis[35] specifically assessed the efficacy and safety of consolidation with VTD or TD. Before starting consolidation, there was no significant difference in CR/nCR rates between the VTD and the TD arms. After consolidation, CR and CR/nCR rates were significantly higher for VTD-treated *versus* TD-treated patients. VTD consolidation significantly increased CR and CR/nCR rates, but TD did not, and 3-year post-consolidation PFS was significantly longer for the VTD group. Thus, VTD consolidation therapy contributed significantly to improved clinical outcomes observed for patients randomly assigned to the VTD arm of the study.

Data from other reports are consistent with the above findings of a clinical benefit of consolidation therapy after ASCT. In a retrospective multicenter study, Leleu *et al.* found that two cycles of VTD consolidation therapy (d=dexamethasone orally 40 mg weekly) resulted in a significantly lower relapse rate compared to no consolidation treatment.[36] In another randomized trial conducted by the Nordic myeloma study group, the use of bortezomib as single-agent consolidation therapy (20 doses during 21 weeks) was compared with no consolidation in a population of bortezomib-naïve patients and proved to be a superior approach.[37]

Finally, the benefit of a second ASCT compared to consolidation therapy and the respective impact of consolidation and maintenance therapies are unknown and randomized studies addressing these questions are underway.

6. What is the impact of maintenance therapy after autologous stem cell transplantation?

In contrast to consolidation therapy which should, by definition, be short term, maintenance therapy is generally assumed to be long term and typically aims to reduce the risk of progression or relapse and to prolong OS. Therefore, maintenance therapy should ideally consist of a 'gentle' treatment for a prolonged period, with long-term safety being a major issue. Given its efficacy in different myeloma treatment settings, and being an oral agent, thalidomide was tested in several randomized trials as a maintenance drug. Although these studies varied in design (dose and duration of thalidomide treatment) most of them showed a significant benefit in terms of response rates (namely CR and/or VGPR) and/or PFS. However, OS was not significantly prolonged in any of the studies while a shorter OS after relapse could be observed in some studies following long-term thalidomide treatment.[38,39] Interestingly, Spencer *et al.* showed both a PFS and OS advantage with prolonged thalidomide treatment (thalidomide + prednisone). In the latter study, thalidomide was delivered for 12 months at 100 or 200 mg daily depending on tolerance.[40] It has been suggested that this benefit may be due to a consolidation rather than a maintenance effect as thalidomide was only administered for 12 months. In the various studies examining prolonged thalidomide treatment, the agent was associated with a high risk of peripheral neuropathy, fatigue, and various other side-effects, all of which represent a serious obstacle for the wider use of the drug in the maintenance setting. Thus, when used in the maintenance setting, one should aim to use a low dose of thalidomide (100 mg daily) and a short duration of treatment (6-12 months) as in the study by Spencer *et al.*[40]

Another oral IMiD, lenalidomide, which is generally better tolerated than thalidomide, was thought to be a potential good candidate drug for maintenance treatment. In the transplant-eligible myeloma population, 2 large placebo-controlled multicenter randomized trials could establish the potential benefit of the long-term use of lenalidomide maintenance. Both studies showed a dramatic improvement in PFS in patients receiving low-dose lenalidomide after ASCT until progression (Table 3).[41,42] In one of these studies (the CALGB study), the longer PFS translated into a significantly longer OS. In both trials, lenalidomide was superior to the comparator arm in all pre-defined prognostic subgroups. Treatment was well tolerated. However, in both studies, an unexpected over-incidence of secondary malignancies (both solid tumors and hematologic malignancies) was described. The pathophysiology of these secondary malignancies remains to be clarified. At present, long-term maintenance with lenalidomide cannot be recommended to all patients because the OS benefit has not yet been widely established and because of the concerns about long-term safety. Furthermore, lenalidomide is currently not approved for maintenance treatment. Ongoing studies are focusing on determining the optimal duration of maintenance therapy and the profile of patients who might benefit most from such a treatment. Indeed, it is likely that the impact of maintenance therapy may prove to be of particular interest in the setting of patients with high-risk disease who usually have a shorter OS and PFS. Preliminary data presented by Kaufman *et al.* suggested that maintenance therapy with lenalidomide and bortezomib may help to alter the natural history of high-risk disease.[43] Obviously, the combined use of both consolidation and maintenance therapies is still controversial and is the subject of ongoing trials.

Bortezomib maintenance therapy has also been investigated in 2 randomized trials (Table 4). In the HOVON 65/GMMG-HD4 trial, patients received bortezomib maintenance for two years after induction with PAD and single or double ASCT, while in the comparator arm, patients received VAD induction followed by high-dose therapy and single or tandem ASCT and thalidomide maintenance for two years.[14] PFS was significantly longer for those patients on the bortezomib arm of the study, while there was no difference in OS. Interestingly, the bortezomib-containing arm resulted in significantly improved PFS and OS in patients with elevated serum creatinine and del(13q4) and del(17p13) compared to the comparator arm. However, because the two arms of the study differed both in the induction and maintenance therapies administered, it is not possible to assign the results to the different maintenance regimens. Rosiñol *et al.* compared randomized patients to maintenance therapy consisting of bortezomib plus thalidomide, thalidomide alone or interferon-α2b after up-front induction with VTD, TD or VBMCP/VBAD+V and high-dose therapy. They observed a significant PFS benefit for VT while there was no significant difference in OS between the arms.[18] Although these results indicate a benefit for bortezomib maintenance therapy, further randomized studies are needed before the use of the agent in the maintenance setting can be recommended. It is worthy of note that the subcutaneous formulation of bortezomib may be an attractive option in the maintenance setting.[44]

7. Which patients are candidates for autologous stem cell transplantation?

Usually, ASCT is indicated for patients under 65 years of age with no severe comorbidities.[3] Two clinical conditions may be discussed.

1. Patients over 65 years of age

ASCT is feasible in selected patients over 65 years of age.[45,46] However, results of published studies are obviously biased by selection criteria. Very few randomized studies have included patients over 65 years of age.[47,48] In these studies, the doses of melphalan were reduced compared to those used in younger patients (100 mg/m^2 instead of 200 mg/m^2) but the transplant procedure was repeated twice. In the Italian study, two courses of melphalan 100 mg/m^2 plus ASCT were superior to the standard chemotherapy regimen melphalan-prednisone (MP).[47] However, the IFM group failed to confirm this result and showed that this approach was inferior to the combination of MP plus thalidomide.[48] Nevertheless, Hailemichael *et al.* recently reported an improved OS with ASCT in selected patients over 65 years of age,[49] suggesting that a careful selection process considering physiological age as a determinant for ASCT would result in better outcomes. Overall in Europe, ASCT is not frequently proposed to patients over 65 years of age and prospective studies are still warranted.

2. Renal impairment

Although ASCT is feasible in patients with renal failure, toxicities of HDT are more frequent and more severe and the doses of melphalan should be decreased.[50,51] Patients with renal failure at time of ASCT are usually excluded from ASCT programs since no randomized trial has been performed in this context. However, renal impairment at presentation does not necessarily mean that ASCT will be contra-indicated after induction therapy and symptomatic measures.

8. Early versus late autologous stem cell transplantation in myeloma?

Until recently, the available research evidence demonstrated that the use of HDT followed by ASCT should be the preferred treatment option for young myeloma patients at diagnosis, since HDT/ASCT was associated with a significant improvement in outcome. However, already in the initial period when HDT/ASCT was compared with conventional chemotherapy, it was noted that while almost all randomized studies showed longer PFS, the OS benefit was less clear, partly because some patients received ASCT as salvage therapy for relapse in the conventional chemotherapy arm.[3] As a consequence, one must acknowledge that ASCT could improve OS whether performed early, as first-line therapy, or late, as rescue treatment.[3,52] Nevertheless, a global consensus was strongly in favor of early front-line ASCT.

Recently, based on the impressive results achieved with novel agents, including those achieved in elderly patients not receiving ASCT, the dogma of mandatory early front-line ASCT *versus* late rescue ASCT in the younger popula-

tion was challenged by many investigators. For instance, the lenalidomide-dexamethasone combination was evaluated by different investigators as primary therapy both in young patients who did not wish to undergo ASCT and in older patients not candidates for ASCT.[53,54] Another study tested the lenalidomide-bortezomib-dexamethasone combination.[55] These studies showed that such modern combinations can yield high complete remission rates and promising PFS estimates. The lenalidomide-bortezomib-dexamethasone combination followed by ASCT appears to be a promising approach leading to a very high rate of ORR (94%) and an impressive long PFS.[56] Moreover, these treatments are quite well tolerated, and may be given for longer periods. Interestingly, patients who did not receive ASCT upfront might still receive it at time of relapse. Therefore, the role of up-front ASCT is being questioned in many centers.[57] Ongoing randomized trials comparing up-front ASCT *versus* novel agents without high-dose therapy and ASCT will provide a definitive answer to this question in the era of modern therapy. In one of these trials, a preliminary analysis suggests that ASCT reduced the risk of progression, while OS was comparable to that in the arm without high-dose therapy.[58] However, longer follow up is needed. It is actually possible that some subgroups of patients may still need up-front ASCT in combination with novel agents, while ASCT may be postponed in some other patients.

9. *Single* versus *tandem transplant?*

In the absence of new treatments in the 1990s, the only possibility to attempt to improve outcome was to further increase dose intensity by developing the concept of double intensive therapy, which was pioneered by the Arkansas group.[59] Three randomized trials showed a benefit in favor of double ASCT in terms of PFS, but 2 of them failed to show an OS benefit.[3] In the trial carried out by Attal *et al.*, double ASCT resulted in an OS benefit in patients who did not achieve a VGPR after the first transplant.[60] In a recently published Cochrane Database systematic review of first-line tandem ASCT *versus* single HDT/ASCT studies, the authors concluded that none of the studies included in the analysis was sufficiently informative to support treatment decisions concerning the question of single *versus* tandem ASCT.[61] In addition, none of the trials included novel agents, which are now considered standard treatment.

Recent results with novel agents appear to suggest that there may be a role for tandem ASCT in high-risk disease defined by the presence of adverse cytogenetic abnormalities. In the trial by the Italian myeloma study group which investigated VTD *versus* TD as induction and consolidation, there was no difference in PFS for patients with or without translocation t(4;14) in the VTD arm, indicating that the combination retained its efficacy in the presence of the high-risk signature.[6] In addition, progression, relapse or death at three years was comparable for patients with or without the translocation. Furthermore, a subgroup analysis of the HOVON65/GMMG-HD4 trial, which compared PAD *versus* VAD induction, HDM and bortezomib or thalidomide maintenance, showed that the adverse impact of del(17p13) on PFS and OS could be significantly reduced by a novel agent induction regimen followed by tandem transplant, followed by novel agent-based maintenance treatment.[62] Although these data suggest a benefit for tandem ASCT in high-risk disease, randomized studies are needed to confirm these observations before recommendations regarding its routine use can be made.

An alternative strategy including tandem ASCT was developed by Barlogie *et al.*: total therapy 3 (TT3). This is a complex treatment approach including induction, tandem ASCT, consolidation and maintenance. This treatment can allow among the best results in myeloma therapy to be achieved, with a CR/nCR rate of 83%, a 2-year EFS of 84% and a 2-year OS of 86%.[63] Furthermore, subgroup analyses showed that the adverse effect of del(17p13) or TP53 deletion on PFS and OS was significantly reduced with TT3.[64,65] Thus, this treatment including tandem ASCT can achieve impressive results even in those patients with adverse cytogenetics. However, one must acknowledge that such results are achieved at the expense of treatment-related death rates of 5%. Thus, patients who will mostly benefit from this treatment still have to be defined. Furthermore, it is still unclear which step of the different sequences of TT3 is most useful.

10. What is the role of autologous stem cell transplantation as salvage therapy?

At time of disease recurrence, there is no one standard salvage approach, but instead, various therapeutic options are available, including novel agent-based therapy, administered for a fixed duration of time or until progression. When a frozen autologous graft is still available, it is also possible to repeat high-dose therapy in patients who previously responded to the front-line application of HDM and ASCT. Over time, several reports have demonstrated the feasibility of this salvage strategy.[66-73] Most data are derived from retrospective studies and are based on experiences with relatively small numbers of selected patients. In this setting, PFS has been shown to range from 7 to 22 months, and the treatment-related mortality was acceptable, ranging from 0 to 8%. Various prognostic factors for prolonged PFS have been described, such as the duration of response to the first HDM.[66,67,71] or the number of lines of therapy prior to salvage ASCT.[70,72] Currently, it is realistic to assume that the repeated administration of HDM with ASCT can be considered as salvage therapy if the interval between prior ASCT and relapse is 1.5-2 years or more. Prolonged duration of remission after the first ASCT is associated with improved PFS and OS after the second ASCT.

Conclusions and future perspectives

Compared to historical results achieved with single or even double ASCT, results of HDT/ASCT have dramatically improved with the addition of novel agents (thalidomide and lenalidomide, bortezomib). These agents have not only improved the CR rates pre- and post-transplant, but they have resulted in tangible improvements in outcome as evidenced by longer PFS and OS. Numerous questions surrounding the transplant setting remain, such as the role for prolonged therapy following transplant, the role of high-dose therapy itself, as well as other practical questions regarding the optimization of the different steps

in the transplant procedure. Ongoing studies are needed to further improve the results obtained with transplantation as part of our quest for more effective and better tolerated therapies.

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References

1. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996;335(2):91-7.
2. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348(19):1875-83.
3. Harousseau JL, Moreau P. Autologous hematopoietic stem-cell transplantation for multiple myeloma. N Engl J Med. 2009;360(25):2645-54.
4. Koreth J, Cutler CS, Djulbegovic B, Behl R, Schlossman RL, Munshi NC, et al. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: A systematic review and meta-analysis of randomized controlled trials. Biol Blood Marrow Transplant. 2007;13(2):183-96.
5. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516-20.
6. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376(9758):2075-85.
7. Moreau P, Avet-Loiseau H, Harousseau JL, Attal M. Current trends in autologous stem-cell transplantation for myeloma in the era of novel therapies. J Clin Oncol. 2011;29(14):1898-906.
8. Barlogie B, van Rhee F, Shaughnessy JD Jr, Anaissie E, Crowley J. Making progress in treating multiple myeloma with total therapies: issue of complete remission and more. Leukemia. 2008;22(8):1633-6.
9. Paiva B, Martinez-Lopez J, Vidriales MB, Mateos MV, Montalban MA, Fernandez-Redondo E, et al. Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma. J Clin Oncol. 2011;29(12):1627-33.
10. Ladetto M, Pagliano G, Ferrero S, Cavallo F, Drandi D, Santo L, et al. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. J Clin Oncol. 2010;28(12):2077-84.
11. Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, van Oers MH, et al. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. Blood. 2010;115(6):1113-20.
12. Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol. 2010;28(30):4621-9.
13. Morgan GJ, Davies FE, Gregory WM, Bell SE, Szubert AJ, Navarro Coy N, et al. Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. Haematologica. 2012;97(3):442-50.
14. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol. 2012;30(24):2946-55.
15. Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orlowski R, Blade J, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. Blood. 2011;117(23):6063-73.
16. Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood. 2011;118(22):5752-8; quiz 982.
17. Rosinol L, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, de la Rubia J, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood. 2012;120(8):1589-96.
18. Rosinnol L, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, De La Rubia J, et al. Maintenance Therapy After Stem-Cell Transplantation for Multiple Myeloma with Bortezomib/Thalidomide Vs. Thalidomide Vs. alfa2b-Interferon: Final Results of a Phase III Pethema/GEM Randomized Trial. ASH Annual Meeting Abstracts. 2012;120(21):334-.
19. Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012;119(19):4375-82.
20. Ludwig H, Viterbo L, Greil R, Masszi T, Spicka I, Shpilberg O, et al. Randomized phase II study of bortezomib, thalidomide, and dexamethasone with or without cyclophosphamide as induction therapy in previously untreated multiple myeloma. J Clin Oncol. 2013;31(2):247-55.
21. Moreau P, Attal M, Pegourie B, Planche L, Hulin C, Facon T, et al. Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. Blood. 2011;117(11):3041-4.
22. Moreau P, Facon T, Attal M, Hulin C, Michallet M, Maloisel F, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. Blood. 2002;99(3):731-5.
23. Anagnostopoulos A, Aleman A, Ayers G, Donato M, Champlin R, Weber D, et al. Comparison of high-dose melphalan with a more intensive regimen of thiotepa, busulfan, and cyclophosphamide for patients with multiple myeloma. Cancer. 2004;100(12):2607-12.
24. Shimoni A, Smith TL, Aleman A, Weber D, Dimopoulos M, Anderlini P, et al. Thiotepa, busulfan, cyclophosphamide (TBC) and autologous hematopoietic transplantation: an intensive regimen for the treatment of multiple myeloma. Bone Marrow Transplant. 2001;27(8):821-8.
25. Lahuerta JJ, Mateos MV, Martinez-Lopez J, Grande C, de la Rubia J, Rosinol L, et al. Busulfan 12 mg/kg plus melphalan 140 mg/m2 versus melphalan 200 mg/m2 as conditioning regimens for autologous transplantation in newly diagnosed multiple myeloma patients included in the PETHEMA/GEM2000 study. Haematologica. 2010;95(11):1913-20.

26. Blanes M, Lahuerta JJ, Gonzalez JD, Ribas P, Solano C, Alegre A, et al. Intravenous busulfan and melphalan as a conditioning regimen for autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: a matched comparison to a melphalan-only approach. Biol Blood Marrow Transplant. 2013;19(1):69-74.
27. Kletzel M, Jacobsohn D, Duerst R. Pharmacokinetics of a test dose of intravenous busulfan guide dose modifications to achieve an optimal area under the curve of a single daily dose of intravenous busulfan in children undergoing a reduced-intensity conditioning regimen with hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2006;12(4):472-9.
28. Lonial S, Kaufman J, Tighiouart M, Nooka A, Langston AA, Heffner LT, et al. A phase I/II trial combining high-dose melphalan and autologous transplant with bortezomib for multiple myeloma: a dose- and schedule-finding study. Clin Cancer Res. 2010;16(20):5079-86.
29. Roussel M, Moreau P, Huynh A, Mary JY, Danho C, Caillot D, et al. Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: a phase 2 study of the Intergroupe Francophone du Myelome (IFM). Blood. 2010;115(1):32-7.
30. Mohty M, Ho AD. In and out of the niche: perspectives in mobilization of hematopoietic stem cells. Exp Hematol. 2011;39(7):723-9.
31. Mohty M, Duarte RF, Croockewit S, Hubel K, Kvalheim G, Russell N. The role of plerixafor in optimizing peripheral blood stem cell mobilization for autologous stem cell transplantation. Leukemia. 2011;25(1):1-6.
32. Bensinger W, DiPersio JF, McCarty JM. Improving stem cell mobilization strategies: future directions. Bone Marrow Transplant. 2009;43(3):181-95.
33. Russell N, Douglas K, Ho AD, Mohty M, Carlson K, Ossenkoppele GJ, et al. Plerixafor and granulocyte colony-stimulating factor for first-line steady-state autologous peripheral blood stem cell mobilization in lymphoma and multiple myeloma: results of the prospective PREDICT trial. Haematologica. 2013;98(2):172-8.
34. Barlogie B, Tricot G, Rasmussen E, Anaissie E, van Rhee F, Zangari M, et al. Total therapy 2 without thalidomide in comparison with total therapy 1: role of intensified induction and posttransplantation consolidation therapies. Blood. 2006;107(7):2633-8.
35. Cavo M, Pantani L, Petrucci MT, Patriarca F, Zamagni E, Donnarumma D, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012;120(1):9-19.
36. Leleu X, Fouquet G, Hebraud B, Roussel M, Caillot D, Chretien ML, et al. Consolidation with VTd significantly improves the complete remission rate and time to progression following VTd induction and single autologous stem cell transplantation in multiple myeloma. Leukemia. 2013;27(11):2242-4.
37. Mellqvist UH, Gimsing P, Hjertner O, Lenhoff S, Laane E, Remes K, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. Blood. 2013;121(23):4647-54.
38. Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood. 2012;119(1):7-15.
39. Ludwig H, Durie BG, McCarthy P, Palumbo A, San Miguel J, Barlogie B, et al. IMWG consensus on maintenance therapy in multiple myeloma. Blood. 2012;119(13):3003-15.
40. Spencer A, Prince HM, Roberts AW, Prosser IW, Bradstock KF, Coyle L, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol. 2009;27(11):1788-93.
41. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1782-91.
42. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770-81.
43. Kaufman J, Nooka A, Muppidi S, Heffner LT, Gleason C, Boise L, et al. Survival outcomes of early autologous stem cell transplant (ASCT) followed by lenalidomide, bortezomid, and dexamethasone (RVD) maintenance in patients with high-risk multiple myeloma (MM). J Clin Oncol. 2012;30(15 suppl).
44. Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol. 2011;12(5):431-40.
45. Badros A, Barlogie B, Siegel E, Morris C, Desikan R, Zangari M, et al. Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years. Br J Haematol. 2001;114(3):600-7.
46. Kumar SK, Dingli D, Lacy MQ, Dispenzieri A, Hayman SR, Buadi FK, et al. Autologous stem cell transplantation in patients of 70 years and older with multiple myeloma: Results from a matched pair analysis. Am J Hematol. 2008;83(8):614-7.
47. Palumbo A, Bertola A, Falco P, Rosato R, Cavallo F, Giaccone L, et al. Efficacy of low-dose thalidomide and dexamethasone as first salvage regimen in multiple myeloma. Hematol J. 2004;5(4):318-24.
48. Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet. 2007;370(9594):1209-18.
49. Hailemichael E, Kaufman JL, Flowers CR, Waller EK, Lechowicz MJ, Langston A, et al. Do Elderly Myeloma Patients Benefit From High Dose Therapy (HDT) and Autologous Stem Cell Transplant (ASCT)?: A Comparative Survival Analysis using SEER Registry. ASH Annual Meeting Abstracts. 2012;120(21):2072-.
50. Badros A, Barlogie B, Siegel E, Roberts J, Langmaid C, Zangari M, et al. Results of autologous stem cell transplant in multiple myeloma patients with renal failure. Br J Haematol. 2001;114(4):822-9.
51. Tosi P, Zamagni E, Ronconi S, Benni M, Motta MR, Rizzi S, et al. Safety of autologous hematopoietic stem cell transplantation in patients with multiple myeloma and chronic renal failure. Leukemia. 2000;14(7):1310-3.
52. Fermand JP, Ravaud P, Chevret S, Divine M, Leblond V, Belanger C, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood. 1998;92(9):3131-6.
53. Niesvizky R, Jayabalan DS, Christos PJ, Furst JR, Naib T, Ely S, et al. BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. Blood. 2008;111(3):1101-9.
54. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010;11(1):29-37.
55. Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010;116(5):679-86.
56. Roussel M, Robillard N, Moreau P, Benboubker L, Hulin C, Marit G, et al. Bortezomib, Lenalidomide, and Dexamethasone (VRD) Consolidation and Lenalidomide Maintenance in Frontline Multiple Myeloma Patients: Updated Results of the IFM 2008 Phase II VRD Intensive Program. ASH Annual Meeting Abstracts. 2011;118(21):1872-.
57. Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies. Blood. 2011;118(12):3205-11.
58. Palumbo A, Cavallo F, Hardan I, Lupo B, Redoglia V, Levin M, et al. Melphalan/Prednisone/Lenalidomide (MPR) Versus High-Dose Melphalan and Autologous Transplantation (MEL200) in Newly Diagnosed Multiple Myeloma (MM) Patients <65 Years: Results of a Randomized Phase III Study. ASH Annual Meeting Abstracts. 2011;118(21):3069-.
59. Barlogie B, Jagannath S, Vesole DH, Naucke S, Cheson B, Mattox S, et al. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. Blood. 1997;89(3):789-93.
60. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003;349(26):2495-502.
61. Naumann-Winter F, Greb A, Borchmann P, Bohlius J, Engert A, Schnell R. First-line tandem high-dose chemotherapy and autologous stem cell transplantation versus single high-dose chemotherapy and autologous stem cell transplantation in multiple myeloma, a systematic review of controlled studies. Cochrane Database Syst Rev. 2012;10:CD004626.
62. Neben K, Lokhorst HM, Jauch A, Bertsch U, Hielscher T, van der Holt B, et al. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. Blood. 2012;119(4):940-8.
63. Barlogie B, Anaissie E, van Rhee F, Haessler J, Hollmig K, Pineda-Roman M, et al. Incorporating bortezomib into upfront treatment for

multiple myeloma: early results of total therapy 3. Br J Haematol. 2007;138(2):176-85.
64. Shaughnessy JD, Zhou Y, Haessler J, van Rhee F, Anaissie E, Nair B, et al. TP53 deletion is not an adverse feature in multiple myeloma treated with total therapy 3. Br J Haematol. 2009;147(3):347-51.
65. Waheed S, Shaughnessy JD, van Rhee F, Alsayed Y, Nair B, Anaissie E, et al. International staging system and metaphase cytogenetic abnormalities in the era of gene expression profiling data in multiple myeloma treated with total therapy 2 and 3 protocols. Cancer. 2011;117(5):1001-9.
66. Alvares CL, Davies FE, Horton C, Patel G, Powles R, Morgan GJ. The role of second autografts in the management of myeloma at first relapse. Haematologica. 2006;91(1):141-2.
67. Fenk R, Liese V, Neubauer F, Bruns I, Kondakci M, Balleisen S, et al. Predictive factors for successful salvage high-dose therapy in patients with multiple myeloma relapsing after autologous blood stem cell transplantation. Leuk Lymphoma. 2011;52(8):1455-62.
68. Elice F, Raimondi R, Tosetto A, D'Emilio A, Di Bona E, Piccin A, et al. Prolonged overall survival with second on-demand autologous transplant in multiple myeloma. Am J Hematol. 2006;81(6):426-31.
69. Burzynski JA, Toro JJ, Patel RC, Lee S, Greene RE, Ochoa-Bayona JL, et al. Toxicity of a second autologous peripheral blood stem cell transplant in patients with relapsed or recurrent multiple myeloma. Leuk Lymphoma. 2009;50(9):1442-7.
70. Olin RL, Vogl DT, Porter DL, Luger SM, Schuster SJ, Tsai DE, et al. Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. Bone Marrow Transplant. 2009;43(5):417-22.
71. Jimenez-Zepeda VH, Mikhael J, Winter A, Franke N, Masih-Khan E, Trudel S, et al. Second autologous stem cell transplantation as salvage therapy for multiple myeloma: impact on progression-free and overall survival. Biol Blood Marrow Transplant. 2012;18(5):773-9.
72. Shah N, Ahmed F, Bashir Q, Qureshi S, Dinh Y, Rondon G, et al. Durable remission with salvage second autotransplants in patients with multiple myeloma. Cancer. 2012;118(14):3549-55.
73. Qazilbash MH, Saliba R, De Lima M, Hosing C, Couriel D, Aleman A, et al. Second autologous or allogeneic transplantation after the failure of first autograft in patients with multiple myeloma. Cancer. 2006;106(5):1084-9.