

# Hematopoietic Stem Cell Transplantation in Multiple Myeloma

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## Key Words

Multiple myeloma, autologous stem cell transplantation, allogeneic stem cell transplantation, thalidomide, bortezomib, lenalidomide

## Abstract

The introduction of novel agents (thalidomide, bortezomib, lenalidomide) is changing the management of patients with multiple myeloma who are candidates for stem cell transplantation. Bortezomib-dexamethasone given as induction treatment before autologous stem cell transplantation is significantly superior to the classical vincristine-doxorubicin-dexamethasone regimen in terms of complete response and very good partial response, both before and after transplantation. Triple combinations with thalidomide and bortezomib plus either cyclophosphamide or doxorubicin also yield excellent response rates, with the combination of bortezomib with thalidomide and dexamethasone seeming to be the most promising. Postautologous transplantation maintenance with thalidomide improves the response rate, progression-free survival, and, in some subgroups, overall survival. However, the optimal dose and duration of administration of thalidomide is not known. Both lenalidomide and bortezomib are being evaluated in this setting. The addition of novel agents before and after autotransplant yields a very high complete response rate and prolonged progression-free and overall survival. However, outstanding results have also been achieved with novel agents without transplantation. Therefore, randomized trials comparing novel agents with and

without early transplantation are awaited. Tandem autologous plus reduced-intensity conditioning allogeneic transplantation have replaced myeloablative conditioning allogeneic transplantation. Despite improved results and decreased toxic death rate, this approach still carries the risk for morbidity and mortality related to graft-versus-host disease and should not be proposed in front-line therapy, especially in patients with no adverse prognostic features. (*JNCCN* 2009;7:961–970)

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## Learning Objectives

Upon completion of this activity, participants will be able to:

- Analyze the efficacy of autologous stem cell transplantation in the treatment of multiple myeloma
- Identify the most effective induction regimen prior to treatment of multiple myeloma with autologous stem cell transplantation
- Describe allogeneic stem cell transplantation for multiple myeloma
- Treat multiple myeloma effectively among otherwise healthy adults

## Autologous Stem Cell Transplantation

Until now, high-dose therapy (HDT) supported by autologous stem cell transplantation (ASCT) has been considered the standard of care for front-line therapy of multiple myeloma (MM) in younger patients with normal renal function, and MM is currently the first indication for ASCT.

However, introduction of the novel agents thalidomide, bortezomib, and lenalidomide is changing the scenario in 2 ways. Firstly, these agents can be added to HDT before or after ASCT to increase the complete remission (CR) rate and prolong first remission duration. Secondly, the use of novel agents as front-line therapy in combination with either dexamethasone or alkylating agents yield CR and progression-free survival rates that are comparable to those achieved with HDT without novel agents. Therefore, whether the addition of ASCT to novel agents is superior to novel agents alone is again a matter of debate.

## ASCT Versus Conventional Chemotherapy: Lessons From Randomized Trials

The Intergroupe Francophone du Myélome (IFM) was the first to conduct a randomized trial showing the superiority of HDT with ASCT compared with conventional chemotherapy in 200 patients younger than 65 years.<sup>1</sup> In this IFM 90 trial, HDT significantly improved the response rate, event-free survival, and overall survival. Similar results were published 7 years later by the British Medical Research Council (MRC).<sup>2</sup> As a consequence of these 2 studies, ASCT became standard care for front-line therapy at least in younger patients (< 65 years of age) with normal renal function and no severe comorbidities.

However, other randomized studies published in the past 10 years were not all were that positive.<sup>3-7</sup>

In all but one study, the CR rate was superior in the HDT arm. In 5 of the 6 studies, this superior CR rate translated into a significant benefit in terms of progression-free survival.<sup>1-5</sup>

Regarding overall survival, the superiority of ASCT was significant in only 3 of 7 studies.<sup>1,2,4</sup> This could be explained partly by the impact of ASCT after relapse in patients initially treated with conventional chemotherapy. Use of ASCT either initially or at relapse was a major factor in the survival improvement described in the 1990s in patients younger than 60 years.<sup>8</sup>

An important finding from the IFM 90 trial was the strong relationship between quality of response and overall survival.<sup>1</sup> Patients experiencing CR or at least very good partial remission (VGPR) had longer overall survival than those who experienced only partial response. The relationship between the magnitude of response and the outcome was confirmed in all subsequent IFM trials<sup>9,10</sup> and by other groups, at least for progression-free survival.<sup>2,11</sup> Based on these findings, response criteria were redefined to introduce the concepts of CR (negative immunofixation) and VGPR ( $\geq 90\%$  reduction of the M-component),<sup>12,13</sup> and CR or at least CR plus VGPR is now considered an objective of any treatment.

Almost all of these randomized studies have been performed in patients 65 years or younger who had normal renal function. The IFM group failed to show a benefit from 2 courses of melphalan followed by ASCT in patients aged 65 to 75 years.<sup>14</sup> Therefore, the use of ASCT in older patients is not indicated outside of a clinical trial. No randomized trial has evaluated the impact of ASCT in patients with renal impairment. Again ASCT should not be performed in patients with end-stage renal failure outside of a clinical trial, because the preparative regimen has a higher toxicity.<sup>15</sup>

## Single Versus Double ASCT

The concept of double ASCT was developed by the Arkansas group in the late 1980s with the objective of further increasing CR.<sup>16</sup> The IFM was the first to conduct a randomized trial comparing single and double ASCT in 599 patients up to 60 years of age.<sup>9</sup> On an intent-to-treat basis, the 7-year event-free and overall survival were significantly improved in the double ASCT arm. The benefit in event-free

but not overall survival was confirmed by 2 other randomized studies.<sup>17,18</sup> However, many investigators considered the benefit of this approach to be marginal, and were concerned by cost and morbidity. Therefore, defining which patients benefited more from this aggressive management seemed important.

In the IFM 94 trial, the only parameter defining patients who did not benefit from double ASCT was response to the first ASCT.<sup>9</sup> In the double ASCT arm, patients with less than VGPR after 1 ASCT had a longer overall survival, whereas those experiencing CR or VGPR after the first ASCT had the same overall survival with or without the second. This finding was confirmed by the Italian group.<sup>17</sup>

Although results of double ASCT were satisfactory for patients with good-risk MM, patients with poor-risk characteristics still did poorly despite this more intensive regimen. As an example in the IFM 99 trial, patients with both a high  $\beta_2$ -microglobulin level and cytogenetic abnormalities associated with poor outcome, either t(4;14) or del(17p), had a median overall survival inferior to 2 years.<sup>19</sup> For those patients, other solutions were clearly needed.

## ASCT in the Era of Novel Agents

### Novel Agents in Combination With ASCT

The introduction of novel agents (thalidomide, bortezomib, and, more recently, lenalidomide) has provided a new opportunity to improve ASCT results. The objective is to improve the CR rate and further upgrade the level of response. Recent results from the Spanish group suggest that achievement of immunophenotypic remission as defined by multicolor flow cytometry is a better indicator of improved outcome than the usual CR.<sup>20</sup> Novel agents have been evaluated both after and before ASCT.

### Novel Agents After ASCT

Because even with double ASCT, almost all patients ultimately experience relapse; maintenance therapy was a logical approach to prolong remission duration. Several groups have tested thalidomide in this setting. Three randomized studies have been published and are summarized in Table 1.<sup>21-24</sup>

Although these studies had different designs, all 3 showed a significant benefit in terms of CR (or CR+VGPR), progression-free survival, and overall survival. Therefore post-ASCT treatment with tha-

**Table 1 Maintenance Therapy with Thalidomide**

Author	Number of Patients	Study Design	Induction with Thalidomide	Dose and Duration of Treatment	CR Rate/ P Value	PFS	OS	PN Grade 3/4	Discontinuation Rate
Barlogie et al. <sup>21,24</sup>	668	Initial randomization Double ASCT	50%	Starting dose 400 mg/d From beginning until progression or adverse event	62% vs. 43% P < .001	5-year: 56% vs. 45% P = .01	5-year: 67% vs. 65%* P = NS	27%	30%
Attal et al. <sup>22</sup>	597	Randomization after double ASCT 3 arms = no further treatment vs. pamidronate vs. thalidomide plus pamidronate	No	Median dose 300 mg/d After ASCT and until progression or adverse event	67% vs. 55% vs. 57% <sup>†</sup> P = .03	3-year: 52% vs. 36% vs. 37% P < .009	4-year: 87% vs. 77% vs. 74% P < .04	7%	39%
Spencer et al. <sup>23</sup>	269	After one ASCT thalidomide plus prednisone vs. prednisone	No	200 mg/d 12 mo after ASCT	65% vs. 44% <sup>†</sup> P < .001	3-year: 42% vs. 23% P < .001	3-year: 86% vs. 75% P = .004	10%	31%

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; NS, not significant; OS, overall survival; PFS, progression free survival; PN, peripheral neuropathy.

\* Updated data:<sup>24</sup> survival curves segregate 5 years after initiation of therapy in favor of thalidomide (P = .09).

<sup>†</sup> Complete response plus very good partial response.

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lidomide does improve outcome.

However, several questions persist, such as whether maintenance therapy benefits all patients. A recent update of the Arkansas study showed a significant overall survival benefit only for patients with cytogenetic abnormalities,<sup>23</sup> but patients with del(13) in the IFM study did not benefit from thalidomide maintenance.<sup>21</sup> Recently completed or ongoing studies will determine whether bortezomib or lenalidomide are more effective than thalidomide, particularly in patients with poor-risk cytogenetics.

Another question is what is the optimal duration of post-ASCT. In these studies, the incidence of severe peripheral neuropathy and treatment discontinuation was clearly related to dose and duration of treatment. Lenalidomide, which has almost no neurologic toxicity, might be an attractive alternative.

Moreover, prolonged treatment with thalidomide might select resistant clones and reduce the efficacy of salvage treatment at relapse.<sup>21,25</sup> Therefore, some of these studies should be updated to rule out this possibility.

Yet another question is whether thalidomide is effective mostly through increasing the CR rate (consolidation effect) or controlling the residual

clone (maintenance effect). In the IFM study, patients experiencing CR or VGPR did not seem to benefit from thalidomide treatment. Preliminary results from the MRC IX trial confirm this finding.<sup>25</sup> Therefore, if the objective of post-ASCT treatment is primarily to increase the quality of response, a long treatment is probably not necessary. If consolidation is needed, a combination might be more active than thalidomide alone. The Italian group recently showed that post-ASCT consolidation with a combination of bortezomib, thalidomide, and dexamethasone (VTD) may improve the level of remission and yield molecular remissions, which might be associated with longer response duration.<sup>26</sup>

### Novel Agents as Induction Treatment Before ASCT

The standard induction therapy in patients who are candidates for ASCT is dexamethasone-based, consisting of either dexamethasone alone or VAD (vincristine, doxorubicin, dexamethasone)-like therapy. The primary objective of novel agents given in this context is to increase CR not only before but also after ASCT. The increased CR rate could be converted into longer event-free and overall survival. Another interest would be to reduce the proportion

**Table 2 Novel Agents for Induction Therapy Before ASCT: Two Drug Combinations**

Author	Type of Trial	Combination	Number of Patients	Response Rate After Induction	Response Rate After ASCT
Cavo et al. <sup>28</sup>	Historical control	TD vs. VAD	200	ORR, 76% vs. 52%; <i>P</i> < .001 CR = NS	NA
Rajkumar et al. <sup>27</sup>	Randomized	TD vs. D	201	ORR, 63% vs. 41%; <i>P</i> = .0017 CR = NS	NA
Macro et al. <sup>29</sup>	Randomized	TD vs. VAD	204	≥ VGPR, 35% vs. 17%; <i>P</i> = .002	≥ VGPR, 44% vs. 42%; <i>P</i> = NS
Harousseau et al. <sup>30</sup>	Randomized	VD vs. VAD	424	ORR, 82% vs. 65%; <i>P</i> = .0003 ≥ VGPR, 39% vs. 16%; <i>P</i> < .0001	CR + nCR, 37% vs. 19%; <i>P</i> < .0001 ≥ VGPR, 57% vs. 38%; <i>P</i> = .003
Rajkumar et al. <sup>31</sup>	Randomized	RD vs. Rd	421	ORR, 82% vs. 70%; <i>P</i> = .007 ≥ VGPR, 52% vs. 42%; <i>P</i> = .006	NA

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; D, dexamethasone; NA, not available; nCR, near-complete response; NS, not significant; ORR, overall response rate; RD, lenalidomide plus high-dose dexamethasone; Rd, lenalidomide plus low-dose dexamethasone; TD, thalidomide/dexamethasone; VAD, vincristine/adriamycin/dexamethasone; VD, bortezomib/dexamethasone; VGPR, very good partial response.

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of patients needing a second ASCT because of less than a VGPR after the first.

**Double Combinations: Thalidomide and Dexamethasone:** Thalidomide was the first novel agent to be used in this setting, in combination with dexamethasone (TD). This combination was compared with dexamethasone or VAD<sup>27–29</sup> in a historical control and 2 randomized studies (Table 2).

In all 3 studies, TD was superior to dexamethasone alone or VAD in terms of response rate or VGPR rate. However, the thalidomide-based regimens did not increase the CR rate before ASCT, which remained very low ( $\leq 10\%$ ). In the French trial, post-ASCT VGPR rates with TD and VAD were similar.<sup>29</sup> Moreover, these combinations with thalidomide induced a high incidence of deep vein thrombosis (DVT). Therefore, the benefit of TD compared with VAD seems to remain modest.

**Bortezomib and Dexamethasone:** The IFM has performed a randomized trial (IFM 2005-01) comparing 4 courses of induction treatment before ASCT with either VAD or bortezomib and dexamethasone (VD) in 482 patients with newly diagnosed MM.<sup>30</sup> Compared with VAD, induction with VD increased not only the overall response rate but also the CR plus near CR and CR plus VGPR rates. More importantly, this higher pre-ASCT efficacy translated into higher post-ASCT CR plus near CR or CR plus VGPR rates.

The VD regimen was well tolerated, with no

more adverse events than with standard VAD, except peripheral neuropathy (VD, 53% for all grades and 9% for grade 3 vs. VAD, 32% and 2.5%, respectively). Stem cell collection after priming with granulocyte colony-stimulating factor alone was sufficient to allow 1 ASCT in 97% of patients. Therefore, VD should now be considered a standard induction treatment before ASCT, against which other more complex regimens should be compared.

**Lenalidomide and Dexamethasone:** In the absence of randomized comparisons with other induction regimens, the role of lenalidomide and dexamethasone is unclear. In clinical trials that have evaluated this combination as initial therapy, only part of the patients were actually candidates for ASCT. However, high response rates (including CR+VGPR rate) after 4 cycles have been reported, particularly when lenalidomide was associated with high doses of dexamethasone.<sup>31</sup> Concerns regarding the hematopoietic quality of stem cell collection in relation to lenalidomide myelotoxicity have been solved by using cyclophosphamide as part of the mobilization regimen.<sup>32</sup>

**Triple Combinations:** The addition of a third agent (cyclophosphamide or doxorubicin) looks very attractive (Table 3). The TAD regimen (thalidomide, doxorubicin, dexamethasone) further increased response rate and was significantly superior to VAD.<sup>33</sup> The TCD regimen (thalidomide, cyclophosphamide, dexamethasone) has been tested in a large random-

**Table 3 Novel Agents for Induction Therapy Before ASCT: Three-Drug Combinations**

Author	Combination	Number of Patients	Response After Induction	Response After ASCT
Lokhorst et al. <sup>33</sup>	TAD vs. VAD	402	ORR, 72% vs. 54%; $P < .001$ $\geq$ VGPR, 33% vs. 15%; $P < .001$	CR, 16% vs. 11%; $P = NS$ $\geq$ VGPR, 49% vs. 32%; $P < .001$
Morgan et al. <sup>34</sup>	RD vs. c-VAD	251	CR, 20% vs. 12% $\geq$ VGPR, 39% vs. 27%	CR, 58% vs. 41% $\geq$ VGPR, 67% vs. 43%
Sonneveld et al. <sup>35</sup>	PAD vs. VAD	300	ORR, 80% vs. 64% $\geq$ VGPR, 41% vs. 17%; $P = .001$	CR + nCR, 15% vs. 4%; $P = .05$ $\geq$ VGPR, 59% vs. 47%; $P = .14$
Cavo et al. <sup>36</sup>	VTD vs. TD	460	ORR, 94% vs. 79%; $P < .001$ $\geq$ VGPR, 62% vs. 29%; $P < .001$	CR, 43% vs. 23%; $P < .001$ $\geq$ VGPR, 76% vs. 58%; $P < .001$

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; c-VAD, cyclophosphamide plus vincristine/adriamycin/dexamethasone; nCR, near-complete response; NS, not significant; ORR, overall response rate; PAD, bortezomib/adriamycin/dexamethasone; RD, lenalidomide plus high-dose dexamethasone; TAD, thalidomide/adriamycin/dexamethasone; TD, thalidomide/dexamethasone; VAD, vincristine/adriamycin/dexamethasone; VGPR, very good partial response; VTD, bortezomib/thalidomide/dexamethasone.

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ized study in the United Kingdom.<sup>34</sup> Preliminary results show high CR plus VGPR rates both before and after ASCT.

The PAD regimen (bortezomib, doxorubicin, dexamethasone) has been compared with VAD in a large randomized trial.<sup>35</sup> Again, the new combination is superior in terms of CR plus VGPR rates both before and after ASCT.

Finally the combinations of 2 novel agents might be even more effective. The Italian group recently showed results of a randomized trial comparing VTD and TD.<sup>36</sup> The CR plus VGPR rates were significantly superior to those achieved with TD both before and after ASCT.

**Summary:** To summarize, induction regimens involving novel agents look promising because they increase the response rate compared with classical regimens like VAD. Currently, VD-containing regimens seem superior to TD because of higher pre- and post-ASCT CR or CR plus VGPR rates. Preliminary results with VD and VTD indicate that this higher tumor burden reduction might translate into prolonged progression-free survival.<sup>30,36</sup> However, longer follow-up is needed before drawing definite conclusions regarding the best induction treatment. Toxicity also should be considered, particularly the risk for peripheral neuropathy associated with bortezomib.

### Novel Agents Before and After ASCT

The Arkansas group investigators have integrated novel agents in their complex and aggressive approaches, including tandem ASCT called Total Therapy programs. The Total Therapy 2 trial randomized patients to receive thalidomide throughout their treatment (induction, consolidation, and maintenance). The thalidomide arm was superior in terms of response (including CR) rate and progression-free survival.<sup>20</sup> Although in the initial report, no significant benefit was seen in overall survival because of a shorter survival after relapse in the thalidomide arm, the updated analysis now shows a survival benefit, which is significant in patients with cytogenetic abnormalities.<sup>24</sup>

More recently, in the Total Therapy 3 program, the same investigators have added bortezomib. Preliminary results show impressive 2-year sustained CR and progression-free survival rates (92% and 89%, respectively).<sup>37</sup> Again, longer follow-up is needed, but an important message is that the addition of

bortezomib might overcome the poor prognosis associated with t(4;14).

In several currently ongoing trials, novel agents are used both before and after (consolidation or maintenance) ASCT. Considering the cost and the potential long-term toxicity of these strategies, evaluating the impact of novel agents at each step of the therapy will be useful.

### Novel Agents in Place of ASCT

Front-line therapy with novel agents is dramatically improving the outcome in patients who are not candidates for ASCT, especially those who are elderly. Several European groups have evaluated the combination of melphalan and prednisone alone<sup>14,38</sup> and with bortezomib<sup>39</sup> or lenalidomide.<sup>40</sup> Combinations of lenalidomide plus dexamethasone have been evaluated in the United States.<sup>31,41,42</sup>

Although most of these studies were performed in elderly patients (age > 65 years), CR plus VGPR rates range from 40% to more than 70%. One study showed a CR rate of 30%, which is even better than the rate achieved in younger patients who underwent single ASCT before the introduction of novel agents.<sup>39</sup>

In the most mature studies, median progression-free survival is approximately 2 years,<sup>14,38,39</sup> and preliminary results with lenalidomide plus dexamethasone show promising progression-free and overall survival data.<sup>31,41</sup> Therefore, some investigators already state that ASCT should no longer be used as front-line therapy, but that stem cells could be collected during the first months of therapy with novel agents and used only as a rescue at relapse or progression.

However, although these results are impressive, they do not necessarily indicate that ASCT should not be given as primary therapy in MM, for several reasons:

- Follow-up is still short in several studies with novel agents.
- In studies with lenalidomide up front, older patients and those unwilling to undergo ASCT are mixed with patients who receive HDT plus ASCT.
- ASCT results have recently improved with double ASCT and with the addition of novel agents.

Therefore, randomized studies comparing novel agents with or without early transplantation are needed.

**Summary:** ASCT was the first improvement in MM

therapy and has dramatically increased overall survival in younger patients.<sup>8</sup> The introduction of 3 active novel agents in the past few years is going to completely change the front-line strategy not only in older patients who are not candidates for ASCT, but also in younger patients.

Post-ASCT thalidomide is already known to prolong progression-free and probably overall survival. Novel agents before ASCT increase the pre- and post-ASCT CR plus VGPR rates. Therefore, these combinations of novel agents with ASCT are hoped to induce very high CR rates, high-quality responses, and prolonged progression-free survival. However, because combinations with novel agents without ASCT also induce high CR rates, randomized studies comparing the best regimen with early ASCT with the best nonintensive regimen with ASCT at relapse could be useful. These studies would also have to address the important question of salvage treatment when several active agents have been used up front.

## Allogeneic SCT

Allogeneic SCT after myeloablative preparative regimen can induce molecular remissions and seems to be the only available therapy with a potential for cure or long-term disease control in at least some patients. However, toxicity is excessively high, with transplant-related mortality of up to 50% in some studies. Therefore, allogeneic bone marrow transplantation after myeloablative conditioning is abandoned by most investigators.<sup>43</sup>

Much of the clinical impact of allogeneic SCT has been attributed to the immunologic effect of donor lymphoid cells, called graft-versus-myeloma (GVM). This antitumor effect of donor-immunocompetent cells, which is unfortunately linked to graft-versus-host disease (GVHD), is the basis of reduced-intensity conditioning (RIC) allogeneic SCT. The principle of RIC allogeneic transplantation is to reduce transplant-related toxicity while harnessing GVM effect.

Preliminary experience showed that RIC allogeneic SCT was possible with reduced transplant-related mortality even in older patients (> 60 years of age) and with matched-unrelated donors.<sup>44</sup> However, investigators quickly noted that relapses were frequent when RIC allotransplants were used in patients with relapsed/refractory disease.<sup>45</sup> These re-

sults suggested that the allogeneic GVM effect is not sufficient and that it remains important to reduce tumor burden. Therefore, RIC allotransplantation is now mostly used after tumor burden reduction with HDT followed by ASCT.

The Seattle group recently updated results obtained with tandem ASCT-RIC allogeneic SCT.<sup>46</sup> Although the CR rate was 59% and transplant-related mortality 11% at 1 year, grade 2 to 4 acute GVHD was 42% and extensive chronic GVHD was 74%. The 5-year progression-free and overall survival were 36% and 64%, respectively.

Large prospective trials comparing double ASCT and tandem ASCT-RIC allotransplantation have been performed in the United States and Europe, but all results are not yet fully available. Although 3 studies were published, the selection of patients, preparative regimen, and GVHD prophylaxis were different.<sup>47-49</sup> The Italian study was the only one to show a significant benefit favoring RIC allogeneic SCT. Although transplant-related mortality is reduced with RIC allogeneic SCT compared with standard myeloablative regimens, it remains at approximately 10% to 15% at 1 year for patients with newly diagnosed MM, and the incidence of chronic GVHD is still very high. Therefore, while waiting for the final results of 2 other large studies from United States and Europe multicenter trials, tandem auto-RIC allotransplantation should not be offered in the up-front setting outside of a clinical trial, especially for patients without adverse prognostic factors, considering the very good results achieved with single or tandem ASCT plus novel agents in this subgroup.

## Conclusions

In the era of novel therapies, several questions regarding the ASCT paradigm should be addressed in clinical trials:

- Best induction therapy
- Role of consolidation versus maintenance
- Type of consolidation (second transplant vs. novel agents)
- Type and duration of maintenance
- Impact of minimal residual disease
- Treatment of poor-risk MM

However, the most important question is the role of ASCT, which should be addressed by randomized trials comparing novel agents plus ASCT with novel

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agents alone (or novel agents plus ASCT at relapse)

Outside a clinical trial, current results show that ASCT plus novel agents apparently yields higher CR plus VGPR rates, which should translate into longer progression-free survival. Therefore, ASCT should still be proposed as primary therapy for patients in good clinical condition and aged up to 65 to 70 years. The standard of care is currently 3 or 4 cycles of induction therapy with a bortezomib-based regimen, high-dose melphalan plus ASCT, or 1 year of maintenance with thalidomide (with substitution of lenalidomide possibly considered in the near future).

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## Autologous Stem Cell Transplantation

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- Which of the following statements about previous research into autologous stem cell transplantation (ASCT) for patients with multiple myeloma (MM) is most accurate?
  - ASCT has not improved event-free survival in studies of MM
  - ASCT has not improved overall survival in studies of MM
  - ASCT has not been studied in randomized trials of patients with MM and renal impairment
  - ASCT appears to be most effective among patients at ages 65 and older
- Which of the following regimens is associated with the best outcomes as induction treatment prior to ASCT?
  - Bortezomib and dexamethasone
  - Thalidomide and dexamethasone
  - Vincristine, doxorubicin, and dexamethasone
  - Lenalidomide and dexamethasone
- Which of the following statements about allogeneic stem cell transplantation (SCT) is most accurate?
  - Toxicity associated with allogeneic SCT has historically been very high
  - Reduced-intensity conditioning (RIC) allogeneic SCT appears most successful for relapsed or refractory disease
  - High-dose therapy should be avoided among candidates for RIC allogeneic SCT
  - RIC allogeneic SCT is considered first-line therapy for MM
- The study authors recommend all of the following as primary treatment options for MM among healthy adults under the age of 65, except:
  - 3-4 cycles of induction therapy with a bortezomib-based regimen prior to ASCT
  - Primary treatment with novel agents instead of ASCT
  - High-dose melphalan plus ASCT
  - 1 year of maintenance therapy with thalidomide

### Activity Evaluation

- |   |   |
|---|---|
| <p>1. The activity supported the learning objectives.</p> <p>Strongly Disagree                      Strongly Agree</p> <p>1            2            3            4            5</p>           | <p>3. The content learned from this activity will impact my practice.</p> <p>Strongly Disagree                      Strongly Agree</p> <p>1            2            3            4            5</p>     |
| <p>2. The material was organized clearly for learning to occur.</p> <p>Strongly Disagree                      Strongly Agree</p> <p>1            2            3            4            5</p> | <p>4. The activity was presented objectively and free of commercial bias.</p> <p>Strongly Disagree                      Strongly Agree</p> <p>1            2            3            4            5</p> |

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