The introduction of novel agents (thalidomide, bortezomib, and lenalidomide) in the frontline therapy of multiple myeloma has markedly improved the outcome both in younger patients who are candidates for high-dose therapy plus autologous stem-cell transplantation (HDT/ASCT) and in elderly patients. In the HDT/ASCT paradigm, novel agents may be used as induction therapy or after HDT/ASCT as consolidation and/or maintenance therapy. It is now possible to achieve up to 70% complete plus very good partial remission after HDT/ASCT and 70% 3-year progression-free survival (PFS). However long-term non-intensive therapy may also yield high response rates and prolonged PFS.

Randomized trials comparing these two strategies are underway. In elderly patients, six randomized studies show the benefit of adding thalidomide to melphalan–prednisone (MP). A large randomized trial has also shown that the combination of bortezomib–MP is superior to MP for all parameters measuring the response and outcome. Finally, the role of maintenance is currently evaluated and a randomized trial shows that low-dose lenalidomide maintenance prolongs PFS.

Key words: autologous stem cell transplantation, bortezomib, lenalidomide, multiple myeloma, thalidomide

introduction
The treatment of multiple myeloma (MM) has dramatically changed in the past few years due to the introduction of new agents mostly immunomodulatory drugs (IMIDs) (thalidomide and lenalidomide, and more recently pomalidomide) and proteasome inhibitors (bortezomib and, more recently, carfilzomib). These agents offer new possibilities in relapsed/refractory MM and have increased overall survival (OS) by prolonging survival after relapse [1]. They are currently used in frontline therapy as well, which is associated with further improvement and changes in treatment paradigms.

MM is a heterogeneous disease with multiple genetic changes. As a consequence, until now there is no targeted therapy and these new agents are used in all prognostic subgroups. Therapeutic decisions remain guided mostly by age and general conditions, and by the presence of renal impairment.

Treatment should be started only in symptomatic MM. In asymptomatic or smoldering MM, long-term treatment with lenalidomide–dexamethasone delays the occurrence of symptomatic MM [2], but the impact on the efficacy of overt MM treatment and on OS is unknown and this approach should not be used out a clinical trial. Initial treatment in symptomatic MM still depends on the feasibility of high-dose therapy plus autologous stem-cell transplantation (HDT/ASCT). For the past 20 years, HDT/ASCT has been the standard of care in younger patients without comorbidities [3] and the first question to be asked when deciding primary treatment should be: is the patient candidate for HDT/ASCT?

treatment of MM in patients who are candidates for HDT/ASCT
The primary objective of HDT/ASCT is to achieve complete response (CR), which was a rare event with conventional dose chemotherapy, or at least very good partial response (VGPR). A number of studies have shown that, in the context of HDT/ASCT, there is a statistical correlation between CR or VGPR achievement and progression-free survival (PFS) or even OS [4, 5].

The introduction of novel agents in the HDT/ASCT paradigm was first aimed at increasing the CR rate or at upgrading the level of CR. This has been obtained by using these agents either before or after HDT/ASCT.

novel agents during induction treatment
In the context of HDT/ASCT, the role of induction treatment is to reduce the tumor burden in order to increase the post-HDT/ASCT CR rate and to improve the hematopoietic stem-cell collection by decreasing plasma cell infiltration. In Europe, the standard induction treatment was generally 3–6 cycles of vincristine–adriamycin–dexamethasone (VAD), which was associated with a good quality of stem-cell collection but with a low pre-HDT/ASCT CR rate (<10%) or CR plus VGPR rate (<20%).

All published studies comparing VAD-based regimens to induction treatment with thalidomide or bortezomib have shown that new regimens induce more responses and, more
importantly, more CR or more CR plus VGPR than VAD [6–10]. Therefore, VAD is no longer considered the standard induction treatment before HDT/ASCT. This superiority appears to be related to a higher response rate in patients with poor prognostic features defined by International Staging System or by poor-risk cytogenetic abnormalities such as t(4;14) or del (17p) by FISH analysis.

Other randomized studies have shown that triple combinations with thalidomide–bortezomib–dexamethasone (so-called VTD regimen) are superior to double combinations with either thalidomide–dexamethasone (TD) or bortezomib–dexamethasone (VD) in terms of the CR rate both before and after HDT/ASCT [11–13]. With this type of induction treatment, it is now possible to achieve up to 70% CR plus VGPR after HDT/ASCT. However, the impact of this higher CR rate on PFS is not precisely known since in these randomized trials novel agents were also administered after HDT/ASCT.

Other triple combinations have been tested such as bortezomib–cyclophosphamide–dexamethasone (VCD), bortezomib–lenalidomide–dexamethasone (RVD), or more recently carfilzomib–lenalidomide–dexamethasone (CRD) and yield very encouraging results but in the absence of randomized trial, their place compared with VTD is not yet known. Quadruple combinations do not appear to be superior to triple combinations and may be more toxic [14].

In the US, lenalidomide–dexamethasone has also been used as induction treatment before HDT/ASCT but has never been compared with other approaches in a randomized trial [14].

**novel agents during preparative regimen**

In a pilot phase II study, four injections of bortezomib have been added to high-dose melphalan (Vel-Mel regimen) as preparative regimen before ASCT without unexpected toxicity [15]. The CR plus VGPR rate was also 70% and the CR rate appeared to be superior to VAD in a case-matched study. However, the impact of this regimen compared with melphalan 200 mg/m² is still unknown in the absence of a randomized trial.

**novel agents as consolidation after HDT/ASCT**

Consolidation therapy is a short treatment with the objective of increasing the CR rate after HDT/ASCT or to upgrade the level of CR.

In a randomized study from the Nordic group, bortezomib administered after HDT/ASCT increased the CR rate compared with no further treatment [16].

The Italian group showed that in patients who were already in VGPR after HDT/ASCT, four courses of VTD increased the CR rate from 15% to 49%. Moreover, PCR showed that molecular remissions could be obtained in 18% of cases and PFS was significantly longer in patients with molecular remission [17].

The Gruppo Italiano Malattie EMatologiche dell’Adulto (GIMEMA) group used VTD for both induction and consolidation and showed that this combination was significantly better than the same regimen without bortezomib (TD) [10]. Finally, the Intergroupe Francophone du Myelome (IFM) group tested RVD for induction and consolidation in a pilot phase II study and obtained 48% CR including 38% stringent CR [18].

**novel agents as maintenance after HDT/ASCT**

The objective of long-term maintenance is to control the malignant clone. The ideal maintenance treatment should be oral and well tolerated. Thalidomide was the first to be tested in this indication. Five randomized studies (versus no further treatment) have been published [19–23]. Although the study design and the dose and duration of thalidomide treatment were variable, all studies showed a significant benefit in terms of CR (or CR + VGPR) rate and/or PFS. However, OS was significantly prolonged in only two of the five studies, due to a shorter OS after relapse in the thalidomide groups. A recent meta-analysis confirms that thalidomide maintenance significantly prolongs PFS [23]. It should be noted that since salvage therapies at relapse are becoming more effective, differences in OS may appear late [23, 24]. One important concern is that it is currently impossible to determine which patients may benefit from thalidomide maintenance. In the Arkansas group study, patients with cytogenetic abnormalities by conventional karyotyping had a better OS in the thalidomide group [24], while in the British MRC trial, OS was shorter in the thalidomide group for patients with adverse genetic abnormalities [23]. Finally, prolonged treatment with thalidomide was associated with a high risk of peripheral neuropathy and fatigue, and the optimal duration of thalidomide maintenance is unknown.

Therefore, lenalidomide, which is better tolerated than thalidomide, is a good candidate for maintenance treatment. Two placebo-controlled randomized studies from the cancer acute leukemia group B (CALGB) and from the IFM have recently been completed, and both studies show a dramatic improvement of PFS in patients receiving low-dose lenalidomide after HDT/ASCT until progression [24, 25]. In the CALGB, this longer PFS translated into a significantly longer OS. In both trials, lenalidomide was as superior in all pre-defined prognostic subgroups. Treatment was well tolerated, although in the French study, an unexpected over-incidence of secondary malignancies (both solid tumors and hematologic malignancies) was described.

Bortezomib is less attractive for maintenance therapy since it is administered i.v. but bi-monthly injections are currently evaluated by the Dutch group.

**novel agents before and after HDT/ASCT**

A number of groups are evaluating novel therapies prescribed both before and after HDT/ASCT. The most mature results come from the Arkansas group investigators. They have integrated novel agents in their complex approach, including tandem ASCT called total therapy programs. In the total therapy 2 program, patients were randomly assigned to receive thalidomide throughout their treatment. Thalidomide appeared to increase the response rate, the PFS and the long-term OS [24]. More recently in the total therapy 3 program, the same group has added bortezomib to induction and consolidation. Current results show an impressive CR rate of >90% and 5-year PFS and OS rates of 71% and 78%, respectively [26]. These results appear to be the best ever achieved in MM. Whether such a complex and potentially toxic strategy is needed in all patients will be clarified by the recently completed trials. More recent results confirm that the use of
novel agents as induction and as consolidation and/or maintenance appears to improve the PFS in the HDT/ASCT paradigm and that 3-year PFS superior to 70% are now achievable [11, 27]. Moreover, this strategy is useful and feasible in older fit patients [26]. Several investigators suggest that the addition of bortezomib for induction and consolidation therapy might partially overcome poor prognosis associated with t(4;14) and del(17p) [28–30]. However, the respective impact of induction, consolidation and maintenance is not yet known.

At the same time, frontline therapy with novel agents is markedly improving the outcome in patients who are not candidates for HDT/ASCT. Combinations with lenalidomide–dexamethasone have been evaluated by US investigators as primary therapy both in young patients who did not wish to undergo HDT/ASCT and in older patients. These studies show that treatments with lenalidomide–dexamethasone [31, 32] or more recently with lenalidomide–bortezomib–dexamethasone [33] may also yield very high CR plus VGPR rates and encouraging PFS. Since these treatments are well tolerated, they may be given for long periods of time and it appears that, with prolonged treatment, the response rates continue to improve. Moreover, patients who have not received HDT upfront might receive it at the time of relapse. As a consequence, the place of HDT/ASCT is again challenged and some investigators suggest that frontline treatment with HDT/ASCT should be abandoned. The only way to determine whether HDT/ASCT plus novel agents is still superior to novel agents without intensive treatments (plus HDT/ASCT at progression/relapse) is to perform randomized trials, which are actually ongoing. One important question to be addressed by these studies will be to determine in which subgroups of patients upfront HDT/ASCT is superior and remains necessary.

To conclude, the use of novel agents in the frontline therapy of younger patients with MM markedly improves the outcome. However, bortezomib and lenalidomide are not yet approved in patients with newly diagnosed MM over the age of 65. The second agent to be combined with MP has been bortezomib. The large randomized Vista trial has compared MP and bortezomib plus MP (VMP) [41, 42]. VMP was significantly superior to MP for all parameters measuring response and outcome, including OS. An important finding is that the complete response (CR) rate was 30%, quite comparable to that achieved with HDT in younger patients. Therefore, VMP is also a new EMA-approved standard of care in elderly patients.

dexamethasone-based combinations

The combination of TD was compared with MP in a randomized study in elderly patients [43]. While the response rate including the CR rate was superior in the TD arm, there was no benefit in terms of PFS and OS was significantly shorter in the TD arm due to a higher toxicity and a lower compliance in the TD arm. In this study, both the dose of thalidomide and the dose of dexamethasone were probably too high in patients older than 75 or with poor performance status. The optimal dose of dexamethasone to be combined with immunomodulatory drugs in the frontline therapy of MM was the purpose of a randomized study published by the ECOG group comparing lenalidomide plus high-dose dexamethasone (40 mg for 4 consecutive days three times a month) versus lenalidomide plus low-dose dexamethasone (40 mg weekly) [31]. The results with low-dose dexamethasone were so positive that this combination has become another standard of care for elderly patients.

maintenance therapy after induction treatment

With MPT primary therapy, there is no current evidence that thalidomide maintenance further increases PFS, since in none of the randomized trials evaluating MPT this question was specifically addressed. It should be noted that, in the two IFM studies, the better PFS translated in an OS benefit despite the absence of maintenance therapy, while in the other four randomized trials maintenance thalidomide was proposed and in only one the OS benefit was significant. However, three recent studies suggest that maintenance therapy may improve the outcome in elderly patients as well.
The most convincing is the MM015 randomized trial which compared nine cycles of MP, nine cycles of MP plus lenalidomide (MPR) and nine cycles of MPR followed by low-dose lenalidomide maintenance (MPR-R) [44]. The MPR-R arm was dramatically superior to the other two in terms of PFS. However, until now there is no OS benefit in the lenalidomide maintenance arm.

An Italian randomized trial showed that four drug induction therapy (MPT plus bortezomib) followed by a maintenance therapy with bortezomib plus thalidomide significantly increased both the response rate and 3-year PFS compared with the new standard regimen VMP [45]. A randomized Spanish study also used maintenance therapy with bortezomib–thalidomide or bortezomib–dexamethasone and showed further increase of the CR rate during maintenance therapy may improve results achieved by induction treatment.

how to select among available options in elderly patients?

In elderly patients, the first question is to evaluate the feasibility of novel combinations. Patients over the age of 75 or frail patients with multiple comorbidities may not tolerate full doses. Therefore, regimens with attenuated doses of chemotherapy and dexamethasone and administration of bortezomib on weekly schedules to reduce neurologic toxicity have been proposed [46, 47]. In frail patients, geriatric assessment is necessary before any therapeutic decision [48].

The second question is to choose between the different regimens that have been recently developed. A large randomized trial has compared lenalidomide plus low-dose dexamethasone with MPT, but results are not yet available. In the absence of randomized studies comparing these regimen, the choice largely depends on practical reasons (i.e. versus oral administration) and on the presence of adverse genetic abnormalities (bortezomib usually preferred in patients with poor-risk abnormalities).

patients with renal impairment

Renal impairment is a common complication of MM, which is associated with a more severe prognosis. Rapid intervention to reverse renal dysfunction is critical for the management of these patients, particularly for those with light chain cast nephropathy. Bortezomib with high-dose dexamethasone is considered as the treatment of choice [49, 50]. There is limited experience with thalidomide in patients with myeloma with renal impairment. Lenalidomide is effective in this setting and can reverse renal insufficiency in a substantial subset of patients, when it is given at reduced doses, according to renal function [49]. The role of plasma exchange in patients with suspected light chain cast nephropathy and renal impairment is controversial and high-cutoff hemodialysis membranes have to be better evaluated in this context. Although HDT/ASCT with high-dose melphalan (140 mg/m2) may be feasible in patients with acute renal failure, the impact of this strategy has never been evaluated in a randomized trial.

disclosures

JLH: Honoraria: Celgene, Janssen, Millenium, Onyx.

references


