

Maintenance therapy in multiple myeloma

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Introduction

The treatment of multiple myeloma (MM) has changed dramatically in the past twenty years with the introduction of high-dose therapy plus autologous stem-cell transplantation (ASCT) in younger patients and, more recently, of three novel agents (thalidomide, bortezomib, and lenalidomide).

When conventional chemotherapy was the only available possibility, complete responses (CR) were very rare and the objective of maintenance was to prolong remission duration by continuing the same type of treatment that induced the initial response. With recent therapeutic improvements, CR achievement becomes a realistic goal that, in most cases, is significantly correlated with the outcome.¹ Therefore, both the nature and the impact of maintenance therapy have changed. Maintenance therapy is based currently on novel agents, and its objective is not only to control the clone but also to further decrease the tumor burden and improve the quality of response.

A number of randomized studies show a benefit from maintenance therapy with novel agents (until now, mostly thalidomide), at least in terms of response rate and progression-free survival (PFS). However, there is still a debate as concerns the impact on overall survival (OS) and the optimal administration of maintenance therapy.

Maintenance therapy in the pre-thalidomide era

In patients initially treated with conventional chemotherapy, maintenance chemotherapy has failed to demonstrate any significant benefit.^{2,3} Therefore, the recommendation was to stop chemotherapy once stable response had been achieved (the so-called *plateau* phase).

One study showed a survival advantage for patients receiving alternate-day prednisone maintenance therapy at a dose of 50 mg when compared with 10 mg after standard induction chemotherapy.⁴

In the nineteen-eighties α -interferon maintenance therapy represented a great hope. Following the initial randomized study show-

ing prolonged remissions with α -interferon maintenance in patients responding to conventional induction therapy,⁵ a number of randomized trials were performed but their results were controversial.⁶ Two meta-analyses of randomized trials showed that with interferon maintenance, time to PFS and OS was increased by four to seven months.^{7,8} However, most investigators considered that the benefit was small and needed balancing against cost and potential toxicity of prolonged treatment with α -interferon.

In addition, α -interferon has been used after ASCT, with the hypothesis that it might be more effective in patients with minimal residual disease. In a retrospective analysis of the European Bone Marrow and Blood Transplant Registry, interferon maintenance was associated with improved PFS and OS in patients responding to high-dose therapy.⁹ However, two randomized trials failed to confirm this result.^{10,11}

Thalidomide as maintenance therapy after autologous stem-cell transplantation

When thalidomide maintenance therapy was first introduced in the field of ASCT for MM, the median duration of response did not exceed three years and almost all patients did relapse ultimately.¹² Six randomized trials have evaluated the impact of thalidomide maintenance after ASCT in MM.¹²⁻¹⁷ However, these trials differed in their design and in the dose and duration of thalidomide maintenance (Table 1).

In two of these studies, patients were randomized initially to receive thalidomide throughout their treatment (both before and after ASCT).^{13,17} Therefore, the putative impact of thalidomide was not expected to be a result of the maintenance effect only.

In the other four studies, patients were randomized after ASCT to receive either thalidomide or not. While in two of these trials the control group was to receive no further treatment,^{12,16} in the Tunisian study by Abdelkefi *et al.* (2008), thalidomide maintenance was compared to a second ASCT,¹⁴ and in the Australian study by Spencer *et al.* (2009) the combination of thalidomide plus alternate-day prednisone was compared to the administration of prednisone alone.¹⁵

In two of these trials, patients were randomized only if they were not progressing after induction treatment plus ASCT,^{12,15} while in the other two studies, all patients were randomized, whatever the degree of post-ASCT response.^{14,16} Finally, in the French and Australian studies by Attal *et al.* (2006) and

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Spencer *et al.* (2009), respectively,^{12,15} thalidomide was not used during induction treatment. In the British study by Morgan *et al.* (2008), there was an initial randomization at diagnosis (thalidomide versus no thalidomide),¹⁶ and in the Tunisian study by Abdelkefi *et al.* (2008), all patients received thalidomide plus dexamethasone as induction treatment prior to ASCT.¹⁴

In four of these six trials, thalidomide was prescribed until relapse or until severe adverse event, while in the studies by Abdelkefi *et al.* (2008) and Spencer *et al.* (2009), the duration of thalidomide was fixed (six months in the Tunisian study and 12 months in the Australian study).^{14,15} The daily dose of thalidomide varied from 100 mg/day¹⁴ to an initial dose of 400 mg/day in the first two of the six studies.^{12,13} Despite these disparities, all six studies showed a benefit in favor of thalidomide in terms of response rate (CR, or greater than or equal to very good partial remission and PFS) (Table 2).

Results are not that clear-cut as regards OS. While in the initial publication of the French and Tunisian studies^{12,14} OS was significantly longer in the thalidomide trials, with longer follow-up this survival advantage disappeared, and Abdelkefi *et al.* (2009) did publish a retraction recently.¹⁸

On the contrary, the first publication from the Arkansas group showed no significant difference in OS between the two groups, because of a shorter OS after relapse in patients initially treated with thalidomide.¹¹ However, with a longer follow-up, the OS curves diverge after five years.¹⁹ A second report of the same trial, showed a trend in favor of thalidomide and a significant benefit in the subgroup of patients with karyotypic abnormalities.¹³ In the Dutch (Lokhorst *et al.*, 2008) and British (Morgan *et al.*, 2008) studies, the PFS benefit did not translate into a significant OS benefit, again because of a shorter OS after relapse in the thalidomide group.^{16,17}

Table 1. Post-ASCT maintenance with thalidomide: randomized studies.

Author	Induction	ASCT	Thalidomide administration	Design
Attal <i>et al.</i> ¹²	No Thal	Double	Starting dose 400 mg/d until relapse	After ASCT (if no progression) No treatment vs. Thal + Pamidronate
Barlogie <i>et al.</i> ¹³	50% Thal	Double	Starting dose 400 mg/d until relapse	Initial randomization Thal vs. no Thal
Abdelkefi <i>et al.</i> ¹⁴	Thal	Single + Thal vs. double	100 mg/d for 6 months	After ASCT
Spencer <i>et al.</i> ¹⁵	No Thal	Single	20 mg/d for 1 year	After ASCT (if no progression)
Morgan <i>et al.</i> ¹⁶	50% Thal	Single	100 mg/d until relapse	After ASCT
Lokhorst <i>et al.</i> ¹⁷	50% Thal	Double	200 mg/d until relapse	Initial randomization TAD → Thal VAD → IFN

ASCT, autologous stem cell transplantation; Thal, thalidomide; d, day; TAD, thalidomide adriamycin dexametason; VAD, vincristine adriamycin dexametason; IFN, interferon.

Table 2. Results of randomized studies on post-ASCT maintenance with thalidomide.

Author	N. of patients	Median follow-up	Response rate	PFS or EFS	OS initial publications	OS updated results
Barlogie <i>et al.</i> ¹³	668	42 m	62% vs. 43% $p < 0.001$	5-year EFS 56% vs. 44% $p = 0.01$	5-year OS 65% vs. 65%	$p = 0.09$
Attal <i>et al.</i> ¹²	597	40 m	*67% vs. 55% or 57% $p = 0.03$	3-year EFS 52% vs. 37% $p = 0.002$	4-year 87% vs. 75%	NS $p = 0.04$
Abdelkefi <i>et al.</i> ¹⁴	195	33 m	*68% vs. 54% $p = 0.04$	3-year PFS 85% vs. 57% $p = 0.02$	3-year 85% vs. 65%	NS $p = 0.04$
Spencer <i>et al.</i> ¹⁵	269	3 y	65% vs. 44%* $p < 0.001$	3-year PFS 42% vs. 23% $p < 0.001$	3-year 86% vs. 75% $p < 0.004$	ND
Morgan <i>et al.</i> ¹⁶	820**	32 m	NA	Better in patients with < VGPR $p < 0.007$	NS Median OS	ND
Lokhorst <i>et al.</i> ¹⁷	556	52 m	*66% vs. 54% $p = 0.005$	Median EFS 34 m vs. 22 m $p < 0.001$	73 m vs. 60 m $p = 0.77$	ND

*, complete response; +, very good partial response (VGPR); **, including patients receiving non-intensive induction; ASCT, autologous stem cell transplantation; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; NS, not significant; m, months; y, years; ND, not done; NA, not available.

How can we analyze these differences?

The first message is that OS data should not be analyzed and published too early. In the past the only possibility at relapse was conventional chemotherapy. Currently we have more possibilities (e.g., ASCT, thalidomide and lenalidomide, bortezomib), and survival after relapse may be longer than duration of first response. Since it is possible to achieve median OS of more than or equal to five years now, OS should not be analyzed before at least five-year median follow-up time.

Secondly, OS obviously depends on salvage treatments. If thalidomide is prescribed until relapse or severe toxicity, one can imagine that thalidomide should not be used at relapse. Therefore, more patients receive thalidomide at relapse in the no-thalidomide trials, and the design of these studies is rather early (up front) thalidomide versus late (at relapse) thalidomide. This was actually the case with ASCT: in randomized trials comparing ASCT

and conventional chemotherapy, ASCT was superior in terms of PFS but not always in terms of OS, partly because patients in the conventional chemotherapy group could receive ASCT at relapse.²⁰ A randomized study comparing early versus late ASCT showed no significant difference in terms of OS.²¹

Moreover, the risk of thalidomide-induced peripheral neuropathy is clearly related to the cumulative dose, and prolonged exposure carries the risk of severe neuropathy, precluding or limiting the use of bortezomib. Prolonged exposure to thalidomide might select clones resistant not only to thalidomide but also to other agents. We already know that lenalidomide is less effective in patients resistant to thalidomide than in thalidomide-naïve patients.²²

Finally, salvage treatment depends on the availability of novel agents. When the British trial by Morgan *et al.* (2008) was performed, there was a limited access to bortezomib, and lenalidomide was not available except for clin-

ical trials. Therefore there were more therapeutic possibilities (including thalidomide) at relapse in the no-thalidomide group.

These considerations clearly raise the issue of the optimal duration of maintenance therapy. Should it be fixed as in the Tunisian or Australian studies,^{14,15} or unlimited as in the other four studies?^{12,13,16,17} The theoretical interest of prolonged maintenance is to further improve the level of tumor burden reduction, hence prolonging PFS but, on the other hand, this benefit might be hampered by reduced salvage possibilities, hence a shorter OS after relapse. A randomized study addressing this question might be extremely useful.

Additional questions

What is the optimal schedule of administration?

In the first two studies by Attal *et al.* (2006) and Barlogie *et al.* (2006), the initial daily dosage was high (400 mg) and the duration of

treatment was unlimited, which explains the high incidence of severe neuropathy (Grade ≥ 3), as well as the percentage of patients who discontinued treatment because of toxicity.^{12,13} Although no randomized study has compared different schedules of administration, doses of 100 mg or 200 mg/day during 6-12 months appear to be effective and better tolerated.^{13,14}

Is thalidomide maintenance useful for all patients, and are we able to predict patients who will benefit from maintenance therapy?

Unfortunately there is no clear response to this question. In the French study by Barlogie *et al.* (2006), patients with del¹³ apparently did not benefit from thalidomide maintenance, but at the time of this trial other abnormalities that are frequently associated with del(13), such as t(4;14) or 17p del, were not routinely studied.¹² We know now that the negative prognostic impact of del(13) is mostly a result of these two additional abnormalities.²³ We have no published data on the impact of thalidomide in this subgroup of patients with these poor-risk abnormalities, although in a preliminary report (Lokhorst *et al.*, 2008), thalidomide appeared to perform poorly in patients with del(17p).¹⁷

In the updated analysis of the Arkansas study by Adelkefi *et al.* (2009), thalidomide significantly improved OS of patients with cytogenetic abnormalities as defined by conventional karyotyping.¹⁸ This heterogeneous subgroup of patients generally is considered as poor-risk, since the possibility of studying mitoses is associated with a more proliferative disease.

Finally, in the studies by Attal *et al.* (2006) and Morgan *et al.* (2008), only patients who did not achieve at least a very good partial response (VGPR) after transplant benefitted from thalidomide maintenance,^{12,16} but this was not confirmed by Spencer *et al.* (2009).¹⁵

Does thalidomide act as a maintenance or consolidation therapy?

In all the studies reviewed, the PFS prolongation was associated with a CR or CR/VGPR increase. Moreover, the fact that patients who showed CR after ASCT did not benefit from thalidomide in at least two of the studies could mean that thalidomide might act more by increasing the post-ASCT CR rate than by controlling the residual clone. In other words, post-ASCT thalidomide might be considered as a consolidation therapy, and might be administered with the objective of further decreasing the tumor burden. If this is true, we still have to determine the optimal level of response. Is CR with negative immunofixation the requested level or should we try to obtain higher levels of response (stringent response, immunophenotypic response, or even molecular response)?

This important question should be addressed in future trials. To date, Paiva *et al.* (2008) have shown that immunophenotypic CR, as assessed by multi-parameter flow cytometry, is associated with a better outcome than CR as defined only by immunofixation.²⁴

Other novel agents as maintenance therapy after autologous stem-cell transplantation

Lenalidomide, which is better tolerated than thalidomide and can be prescribed safely for long periods of time, appears to be an ideal candidate for maintenance therapy. However, this agent is more myelotoxic than thalidomide and the optimal dose of lenalidomide after high-dose therapy is not known. Two large randomized trials from the Intergroupe Francophone du Myelome (IFM) and the Cancer and Acute Leukemia Group B (CALGB) groups have tested lenalidomide as maintenance after ASCT, but results of these studies are not available.

In addition, bortezomib has been evaluated in this setting by Morgan *et al.* (2008) and Paiva *et al.* (2008).^{16,24} Since bortezomib is associated with a high incidence of peripheral neuropathy when used on a bi-weekly schedule at a dose of 1.3 mg/m², the issue of the toxicity/efficacy ratio is crucial.

If the objective of post-ASCT therapy is to increase the level of response with a consolidation effect further, short-term treatment with combinations of novel agents might be attractive as well. Ladetto *et al.* (2008) recently showed encouraging results with four courses of consolidation treatment with bortezomib-thalidomide-dexamethasone.²⁵ In this study, six out of 24 patients, who were at least in VGPR after ASCT, achieved molecular remissions and none of them had a relapse with a median follow-up of 26 months.

Novel agents as maintenance therapy after allogeneic stem-cell transplantation

Currently, allogeneic stem-cell transplantation (allo-SCT) following a myeloablative conditioning regimen has almost been abandoned in MM because of excessive toxicity.²⁶ Reduced-intensity conditioning is associated with reduced transplant-related mortality but with increased relapse rate compared to standard allo-SCT.²⁷ In order to decrease the relapse rate, a strategy with tandem ASCT-reduced intensity conditioning allo-SCT is currently

proposed. However, relapses remain frequent, especially in the absence of chronic-graft versus host disease.²⁶ Therefore, post-transplant immunotherapy with donor-lymphocyte infusions and/or novel agents has been tested with the objective of upgrading the level of response. In a preliminary experience, Kroger *et al.* (2009) have proposed novel agents (thalidomide, bortezomib, or lenalidomide) to patients who were not in CR after allo-SCT and donor lymphocyte infusions.²⁸ They could convert partial remission to CR in 59% of patients and to molecular remissions in 50% of patients.

Thalidomide maintenance therapy after non-intensive induction treatment

In a recent trial Ludwig *et al.* (2009) evaluated thalidomide plus interferon compared with interferon alone in 135 elderly patients with at least stable disease after induction treatment with either thalidomide dexamethasone or melphalan-prednisone (MP). Although PFS was significantly longer in the thalidomide group (24 months versus 13 months, $p > 0.024$), OS was similar in both groups.²⁹

Five randomized trials have compared MP and MP plus thalidomide (MPT) as the primary treatment in elderly patients.^{30,35} Although the design of these studies and the inclusion criteria were slightly different, all five studies have shown a benefit of MPT in terms of response rate, and PFS was significantly longer in the MPT groups of four out of five studies (Table 3).

However, in only two studies this benefit translated into a significantly longer survival,^{32,33} and in these two studies there was no maintenance while in the other three trials there was a maintenance with thalidomide alone in the MPT groups. In the Italian study by Palumbo *et al.* (2008), the shorter survival after relapse in the MPT group might have been explained by a lower percentage of patients receiving thalidomide as salvage treatment at relapse.³¹ Since the three studies were not designed to address the question of maintenance, it is not possible to consider that the lack of survival benefit in the MPT group is related to maintenance thalidomide. However, one can conclude from these studies that there is no evidence that maintenance thalidomide is useful in elderly patients initially treated with MPT. Until now, in elderly patients, available data do not show a benefit from maintenance treatment with thalidomide, at least in terms of OS. At least two randomized studies addressing the question of maintenance treatment with lenalidomide in elderly patients are ongoing.

Table 3. Melphalan-prednisone versus melphalan-prednisone-thalidomide studies: absence of impact of maintenance with thalidomide on overall survival.

Author	Palumbo <i>et al.</i> ³¹	Facon <i>et al.</i> ³²	Hullin <i>et al.</i> ³³	Golbrandsen <i>et al.</i> ³⁴	Wijermans <i>et al.</i> ³⁵
Number of patients (MPT)	331 (167)	447 (125)	232 (113)	362 (182)	301 (152)
Age (yrs)	72	69	78.5	74.5	72
Median range	60-85	65-75	76-91	49-92	-
WHO ^{3/4} (%)	5	8	7	30	4
MPT regimen					
Number of cycles	6	12	12	Until plateau	Until plateau
M dosing	4 mg/m ² d1-7	0.25 mg/kg d1-4	0.2 mg/kg d1-4	0.25 mg/kg d1-4	0.2 mg/kg d1-5
T dosing	100 mg/d	Up to 400 mg/d	100 mg/d	Up to 400 mg/d	200 mg/d
Maintenance	YES	NO	NO	YES	YES
Outcome (MPT vs. MP)					
Response rate (%)	76 vs. 48*	76 vs. 35*	62 vs. 30*	49 vs. 28*	66 vs. 47*
PFS (m)	22 vs. 14.5*	27.5 vs. 18*	24 vs. 19*	20 vs. 18	14 vs. 10*
OS (m)	45 vs. 47.5	51.5 vs. 33*	45 vs. 27.5*	29 vs. 33	37 vs. 30

Significant difference, ($p < 0.005$); d, day; M, melphalan; P, prednisone; T, thalidomide; MP, melphalan-prednisone; WHO, World Health Organization; OS, overall survival; PFS, progression-free survival.

Conclusions

In younger patients, post-ASCT maintenance therapy with thalidomide appears to increase tumor burden reduction further, which translates in prolonged PFS. However, the benefit in terms of OS is not clear and many questions remain regarding the respective role of consolidation versus maintenance, the optimal drug and the optimal schedule of administration and duration of treatment, as well as the characteristics of patients who may benefit from this approach. In elderly patients there is currently no evidence that maintenance treatment improves OS.

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