

Maintenance treatment in multiple myeloma

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Until recently, the interest of maintenance therapy after remission achievement has not been demonstrated convincingly in multiple myeloma (MM).

maintenance after conventional chemotherapy

Maintenance chemotherapy has failed to demonstrate any benefit [1, 2]. Corticosteroid maintenance was found to prolong the duration of response; however, the effect on survival was controversial [3, 4].

Interferon- α represented a great hope in the 1980s but meta-analysis of randomized trials showed a modest increase in progression-free survival (PFS) and a minimal benefit in overall survival (OS) [5, 6]. Considering the cost and the side-effects of long-term treatment with interferon, this approach has been almost abandoned.

Currently conventional chemotherapy is being replaced by combinations using novel agents (thalidomide, bortezomib or lenalidomide). These new combinations are superior to the classical chemotherapy regimens in terms of remission rate, PFS and OS. Interestingly they induce complete remission (CR) rates that are comparable to those achieved with autologous stem cell transplantation (ASCT). However, until now, the optimal treatment duration and the interest of maintenance therapy once maximal response is achieved are unknown. Randomized studies are addressing this question.

maintenance after high-dose therapy

interferon- α

It was hoped that interferon- α could be more effective after ASCT than after conventional chemotherapy since the tumor burden is lower. Although the preliminary results of a small randomized study were in favour of interferon α maintenance after ASCT, the differences with longer follow-up were no longer significant [7]. The end of the story came with the results of the US Intergroup study which failed to show any difference in PFS and OS between interferon and no further treatment in 242 patients responding to either conventional chemotherapy or to ASCT [8].

thalidomide

Four randomized trials have addressed the question of thalidomide maintenance after ASCT. An Arkansas group has

tested the impact of thalidomide in the context of a complex protocol including induction chemotherapy, double ASCT, consolidation therapy and interferon plus dexamethasone maintenance (Total Therapy 2) [9]. Thalidomide was given from initiation of treatment until relapse or toxicity. In the IFM 99-02 trial, patients with standard-risk MM ($\beta 2$ microglobulin <3 mg/l and/or no deletion 13 by Fish) were randomly assigned after double ASCT to receive no further treatment, pamidronate or thalidomide plus pamidronate [10]. A Tunisian study compared double ASCT upfront with single ASCT plus thalidomide maintenance with ASCT at relapse [11]. An Australian study compared post-ASCT maintenance therapy with either corticoids alone or corticosteroids plus thalidomide [12]. The results of these four studies are summarized in Table 1.

- (i) All studies showed a significant benefit in terms of CR (or CR + VGPR) rate and PFS and in three of four OS was significantly prolonged as well.
- (ii) In the IFM 99-02 trial the effect of thalidomide on EFS differed according to the response achieved after double ASCT. Patients who had at least a VGPR did not benefit from thalidomide while patients who failed to achieve at least VGPR had a significantly longer EFS in the thalidomide arm. This could mean that thalidomide mostly acts by further reducing tumor mass after HDT, like a consolidation therapy rather than by a pure maintenance effect. It should be noted that in the other two studies where thalidomide was given only after ASCT, PFS and OS improvement were also associated with an increase in CR rate.
- (iii) Except in the Arkansas study in which thalidomide was given during induction treatment in combination with dexamethasone and chemotherapy, there is no risk of deep-vein thrombosis since the tumor burden is low.
- (iv) The optimum duration of thalidomide maintenance is not known. However, the incidence of peripheral neuropathy observed with thalidomide is cumulative and is related to the duration of treatment. The incidence of grade 3–4 peripheral neuropathy was 27% in the Arkansas study where treatment was prolonged and only 4% in the Tunisian study where thalidomide was given only for 6 months. If thalidomide acts mostly like a consolidation, long-term treatment might not be necessary. Reducing the duration of treatment could decrease not only the incidence of adverse events but also the risk of resistant clone selection and may also improve therapeutic efficacy at relapse.

J.L. Harousseau is in the Speaker Bureau and Advisory Board of Celgene and Ortho Biotech.

Table 1.

Author	n	ASCT	Dose of thalidomide	Duration of treatment	CR rate	PFS	OS	PN	Grade 3–4 (%)
Total therapy 2 [9]	668	Double	Start = 400 mg/day	From the onset until relapse or toxicity	62% versus 43%	5-year 56% versus 44%	5-year 65% versus 65%		27
IFM 99-02 [10]	597	Double	Median = 200 mg/day	Until relapse or toxicity (median 15 months)	67% versus 55% or 57%	3-year 52% versus 36% or 37%	4-year 87% versus 74% or 77%		7
Tunisian study [11]	140	Single	100 mg/day	6 months	67% versus 51%	3-year 85% versus 57%	3-year 85% versus 65%		4
Australian study [12]	243	Single	200 mg/day	12 months	24% versus 15%	2-year 63% versus 36%	2-year 51% versus 80%		10

ASCT, autologous stem cell transplantation; OS, overall survival; PFS, progression-free survival; PN, peripheral neuropathy

(v) In the pioneer study on thalidomide [13] as well in the IFM 99-02 study, patients with chromosome 13 deletions benefit less from this treatment. Preliminary results with bortezomib or lenalidomide suggest that these agents may overcome the poor prognosis associated with this cytogenetic abnormality [14–16]. Therefore these agents are attractive alternatives for post-ASCT treatment and are currently being evaluated in randomized trials.

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