M. Attal

Purpan hospital, Toulouse, France

The role of maintenance treatment in myeloma

Autologous stem cell transplantation (ASCT) is now recommended for young patients as part of the initial therapy or at time of the disease progression. However, almost all patients ultimately relapse and the median duration of response after ASCT does not exceed 3 years.

To prolong the duration of response, maintenance therapy was a logical approach.

The impact of chemotherapy as maintenance after ASCT has never been demonstrated by a randomized trial. In the eighties it was hoped that alpha interferon which prolonged remission duration after conventional chemotherapy could be even more effective in the context of HDT since the tumor burden was lower. Although the preliminary results of a small randomized study were in favour of interferon maintenance after ASCT, the differences with longer follow-up were no longer significant. 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.

Thalidomide has been tested in this setting by several groups. Four randomised studies have been published (Table 1). The Arkansas group has performed a large randomized trial testing the impact of thalidomide in the context of a complex protocol including induction treatment, double ASCT, consolidation therapy and maintenance (Total Therapy 2).[1] In the initial report, CR rate and 5-year EFS were significantly better in the Thalidomide arm (respectively 62% and 43%, 56% and 44%), 5-year OS were exactly the same (65% in both arms). However, an updated analysis of this protocol with a median follow up of 72 months has recently reported a survival advantage in favour of thalidomide. In the IFM 9902 trial, 2 months after double ASCT, 597 patients with standard-risk MM (β_2 microglobuline 3 mg/L or less and/or no deletion 13 by FISH) were randomly assigned to receive no further treatment, pamidronate or thalidomide plus pamidronate.[2] thalidomide increased the CR plus VGPR rate (67% *vs.* 55% and 57% in the other two arms) the 3-year PFS (52% *vs.* 36% and 37%) and the 4-year OS (87% *vs.* 77% and 74%). In this IFM 9902 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

Table 1. Maintenance total therapy with thalidomide after autologous stem cell transplantation.

	N	*Initial dose, mg*	*Maintenance versus no maintenance*		
			CR, %	*EFS or PFS, %*	*OS, %*
Barlogie *et al.*[1]	668	400	62 *vs.* 43	5-year EFS 56 *vs.* 44	+
Attal et al.[2]	597	400	67 *vs.* 55*	3-year EFS 52 *vs.* 36	4-year OS 87 *vs.* 77
Abdelkefi *et al.*[3]	202	200	64 *vs.* 56*	3-year PFS 85 *vs.* 57	3-year OS 85 *vs.* 65
Spencer et al.[4]	243	200	63 *vs.* 40*	3-year PFS 42 *vs.* 23	3-year OS 86 *vs.* 75

thalidomide arm. This could mean that Thalidomide mostly acts by further reducing the tumor mass after HDT, like a consolidation therapy rather than by a pure maintenance effect. The Tunisian study showed that single ASCT plus thalidomide maintenance was superior to double ASCT in terms of CR+VGPR rate, PFS and OS.[3] Finally, the Australian study was also in favour of Thalidomide maintenance in term of response, EFS and OS.[4] Thus in these four studies thalidomide was shown to significantly improve the RR, the EFS and the overall survival. However, the optimum duration of treatment is unknown. The incidence of peripheral neuropathy observed with Thalidomide is cumulative and is related to the duration of treatment. The incidence grade 3 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. Thus, if thalidomide acts mostly like a consolidation, long-term treatment might no be necessary. Reducing duration of treatment could decrease the incidence of adverse events but also decrease the risk of resistant clones selection and improve the therapeutic efficacy at relapse. Finally, since neuropathy is the major limiting factor in the use of thalidomide as maintenance, lenalidomide, the analogue of thalidomide without neurological toxicity, could be an attractive candidate. Two cooperative groups (IFM and CALGB) have initiated randomized trial designed to evaluate the role of revlimid in this maintenance phase.

References

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