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The role of thalidomide as maintenance after autologous stem-cell transplantation in multiple myeloma

A B S T R A C T

Major progress was obtained in the last ten years for treatment of multiple myeloma (MM). High dose chemotherapy with autologous stem – cell transplant (ASCT) and new drugs as thalidomide, lenalidomide and bortezomibe have completely changed the scenario of MM treatment. ASCT becomes the mainstay of MM treatment for patients up to 65 years old. This strategy has been tested in randomized clinical trials and it proven that ASCT can improve overall survival of MM patients. Unfortunately, the large majority of these patients will relapse in few years after ASCT. Strategies of maintenance were developed trying to improve the ASCT results. Thalidomide has been tested in this setting on at least 4 randomized clinical trials with a significant impact on response rate, event free and overall survival.

Introduction

Autologous stem cell transplantation (ASCT) becomes the mainstay of treatment of multiple myeloma (MM) in patients up to 65 years old. ASCT has been shown to improve response rates and prolong progression free survival and overall survival comparing to conventional chemotherapy. Unfortunately, most patients relapse after ASCT, suggesting that additional treatment is needed. Effective strategies for maintenance and/or consolidation were developed trying to improve ASCT results.[1,2]

Thalidomide, an immunomodulatory agent with antiangiogenic properties, was first introduced in MM treatment by the Arkansas Group in 1999.[3] The impressive results obtained in advanced relapse and refractory patients, with acceptable toxicity, led this drug as a potential candidate to be used as maintenance after ASCT.

Clinical trials

At least 3 randomized clinical trials were conducted testing the potential role of thalidomide with or without corticosteroids after ASCT in MM patients.

The "Intergroup Francophone du Myeloma" has conducted a trial (IFM 99-02) where "low risk patients" (with β_2-microglobulin <3 mg/dL and/or absence of chromosome 13 deletion by FISH) were treated with 3-4 cycles of VAD, followed by two consecutive ASCT conditioned with melphalan 140 mg/m^2 and 200 mg/m^2. Two months after ASCT, patients

were randomized to receive no maintenance (arm A), pamidronate (arm B) or pamidornate plus thalidomide at a dose of 400 mg/day (arm C). In terms of response rate the IFM 99-02 showed that maintenance with thalidomide improves overall response rates (CR + VGPR) compared to the others strategies (67% arm C *vs.* 57% arm B *vs.* 55% arm A, p=0.03). The 3-year probability of event-free survival was superior in the thalidomide arm (52% *vs*. 36% in arm A *vs.* 37% in arm B; p<0.009) and the 4-year probability of overall survival was also improved in thalidomide arm (87% *vs.* 74% in arm B *vs.* 77% in arm A). Drug related adverse events, mainly neuropathy grade 3 or 4, led to discontinuation of thalidomide in 39% of patients.[4]

The Tunisian group designed a trial comparing a strategy of a double ASCT (arm A) versus a single ASCT followed by maintenance therapy with thalidomide, 100 mg/day per 6 months (arm B). A total of 195 patients were enrolled in this study (arm A, n=97; arm B, n=98). In both arms patients received a first line therapy with thalidomide + dexamethasone. In an intention-to-treat analysis and a median follow-up of 33 months, authors observed a better 3-year overall survival and progression free survival for patients treated with ASCT plus thalidomide (OS: 65% in arm A and 85% in arm B, p=0.04; PFS: 57% in arm A and 85% in arm B, p=0.02).[5]

In another recently published study, the Australian group reported the results of a clinical trial comparing maintenance with thalidomide + prednisone versus prednisone alone after a single ASCT. There were 269 patients enrolled, 129 received prednisone alone and 114 received 12 months of thalidomide (200 mg/day) plus prednisone. After a median follow – up of 3 years, authors observed an improvement in 3 years PFS and overall survival for the thalidomide group (PFS: 42% *vs*. 23%; p<0.01 and OS: 86% *vs.* 75 %; p=0.004).[6]

Maintenance with thalidomide after ASCT has been also prospective studied by The Brazilian Multiple Myeloma Study Group. From October 2003 to July 2008, 212 untreated patients <70 years old were enrolled in a prospective randomized multicenter study. The treatment consisted of 3 phases: (1) induction with 3-5 cycles of VAD; (2) high-dose cyclophosphamide (4 g/m^2) plus G-CSF for stem cell mobilization; (3) melphalan 200 mg/m^2 and ASCT. On day +60 post ASCT patients were randomized to receive dexamethasone (40 mg/d x 4 days every 28 days) with (arm A) or without (arm B) thalidomide (200 mg daily) for 12 months or until disease progression. The median age was 55 years (27-70) and 52% were male. The median serum β_2 microglobulin was 3.66 mg/dL, and 33% were ISS stage 3, 36% were ISS stage 2 and 24% had deletion of chromosome 13. In July of 2008, 93 patients (44%) were randomized: 54 in arm A and 39 in arm B. Clinical characteristics of each group were similar. The median follow-up from diagnosis was 15 months. PFS in arms A and B were 42% (95% confidence interval [CI] 22-62) and 25% (95% CI 5-45), p=0.07. A multivariate analysis that included baseline serum β-2-microglobulin and deletion of chromosome 13 showed that maintenance with thalidomide was significantly associated with better PFS (hazard ratio 2.43; 95% CI 1.10-5.35; p=0.03). Overall survival was 65% in arm A (95% CI 35-95) and 74% in arm B (95% CI 44-100), p= NS.[7]

Conclusion

Data emerging from 4 randomized clinical trials, despite differences in strategies and in control arm, strongly suggest that thalidomide can improve response rate, event free survival and overall survival after ASCT for patients with MM. Probably the best maintenance strat-

egy is to use lower doses of thalidomide (100-200 mg/day) for a short period of time (6-12 months) to reduce toxicity and to avoid thalidomide resistance.

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