

Selected Summary

Thalidomide and Hematopoietic Stem Cell Transplantation for Multiple Myeloma

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This randomized study was conducted at Myeloma Institute for Research and Therapy at the University of Little Rock, Arkansas USA. The aim of the study was to assess whether the addition of thalidomide to intensive chemotherapy would improve survival. The primary end point was the 5-year event free survival and the secondary end points were complete response and overall survival.

Between October 1998 and February 2004, 668 patients with newly diagnosed progressive or symptomatic multiple myeloma (age ≤ 75 years) and who had received no more than one cycle of prior therapy were enrolled. Prior local radiotherapy for pain control or cord compression was permitted. Eligibility criteria included (i) Southwest Oncology Group performance status of less than 3, unless the score was based solely on bone pain (ii) Adequate cardiopulmonary function.

Patients were stratified according to serum β_2 -microglobulin levels (< 4 mg/L vs ≥ 4 mg/L). The protocol consisted of 4 phases of treatment namely induction, transplantation, consolidation and maintenance. Induction chemotherapy consisted of 4 cycles of chemotherapy: first cycle using vincristine, adriamycin, dexamethasone (VAD), second and fourth cycles using dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) and third cycle using cyclophosphamide, Adriamycin and dexamethasone (CAD). Stem cell harvesting was done during the third cycle.

Following induction, patients underwent high dose chemotherapy with Melphalan IV at 200mg /m² (reduced to 140mg/m² for patients > 70 years old or those with creatinine level

> 2 mg %) twice supported by tandem peripheral stem cell transplantation (> 2 months apart but within 6 months). During consolidation the first 121 patients enrolled were randomized to either DCEP for 4 cycles every 3 months or DCEP alternating with CAD for 4 cycles each. However the protocol was modified such that all the subsequent patients received cisplatin, cyclophosphamide, adriamycin, etoposide and dexamethasone for 4 cycles every 3 months. Maintenance phase consisted Interferon 3 mu subcutaneously 3 times a week plus dexamethasone for 4 cycles every 3 months during the first year followed by only interferon until disease progression or unacceptable side effects. At enrolment, patients were randomly assigned either to a control group (no thalidomide) or to the experimental group (thalidomide). The thalidomide doses were 400 mg daily during induction chemotherapy (withheld on day 5 of cycle 3 of chemotherapy for the collection of peripheral-blood stem cells), 100 mg daily between transplantations, 200 mg daily with consolidation therapy, 100 mg daily during the first year of maintenance therapy, and then 50 mg on alternating days; the drug was given until relapse or adverse events occurred. All patients proceeded to the transplantation phase regardless of the level of response or the lack of response to induction chemotherapy. CSF was administered to support induction and consolidation chemotherapy, except with VAD regimen. All patients in the thalidomide group received low-molecular-weight heparin prophylactically starting in July 2001. The primary objective of the study was to demonstrate an increase in the five-year event-free survival (EFS) rate from 40% in the control group to 50% in the thalidomide group, given a statistical power of 82% and a two-sided p value of 0.05 by the log-rank test.

The baseline characteristics of thalidomide group (n=323) and the controls (n=345) were similar. Overall, 85% of patients received one transplant, 67% received two transplants, 65% started consolidation therapy, and 56% began the maintenance phase. Complete response (CR) rate was higher in thalidomide group (62% vs. 43%, $P < 0.001$). Five-year EFS was also higher in thalidomide group (56% vs. 44%, $P = 0.01$). The cumulative 12-month treatment-related mortality rate was 8% in both groups, but it was significantly higher among patients 65 years of age or older than among younger patients (13% vs 6%, $P = 0.004$), independently of treatment group. Despite a superior EFS rate in the thalidomide group, there was no significant difference between the two groups in overall survival (OS) owing in part to significantly shorter survival after relapse in the thalidomide group than in the control group (median, 1.1 years vs. 2.7 years; $P = 0.001$). The probability of EFS and OS was significantly lower among patients with cytogenetic abnormalities, those with higher lactate dehydrogenase level and those with a serum albumin level of 3.5 G%. Event-free survival and overall survival were significantly longer among patients who had a CR than among those who had a partial or no response. Thalidomide was discontinued due to toxicity within two years after enrollment in 30% of patients, and within four years in 60%. The high incidence of deep-vein thrombosis in the initial phase of the study (34% among the first 162 patients randomized to thalidomide, as compared with 18% among the first 174 patients in the control group; $P < 0.001$). This was not eliminated by prophylactic administration of low-molecular-weight heparin later in the study. Other thalidomide related toxicities included (i) syncopal episodes related to bradycardia in 12% of patients compared to 4% in the control group. (ii) peripheral neuropathy-grade 2 or more (27% vs. 17%, $p < 0.001$)

COMMENTS

There has been a paradigm shift in the management of multiple myeloma in the recent years. From the use of melphalan and prednisolone in initial years, VAD (vincristine,

adriamycin, dexamethasone) has been the standard induction chemotherapy. Recently the combination of thalidomide and dexamethasone is associated with higher response rates and less toxicity. Present randomized study in a large number of patients have confirmed these observations.

In this study,¹ Barlogie et al have investigated the role of thalidomide during all phases of therapy for myeloma along with tandem transplantation. Although the addition of thalidomide led to more complete responses, it was associated with greater toxicity and did not lead to better overall survival. Recently, Cavo et al² performed a retrospective matched case control analysis of 200 patients with symptomatic myeloma who were primarily treated as part of two consecutive studies with Thal-Dex (TD) (n=100) and VAD (n=100) in preparation for autologous stem cell transplantation (ASCT). The RR were 76% and 52% in the Thal-Dex and VAD arms, respectively with similar rates of CR. The difference in the rate of tumour reduction achieved was not significant between the groups. However, the Thal-Dex arm had a more profound reduction in tumour mass as reflected by significantly lower levels of IgG. The major toxicity with VAD was hematologic (grade 3-4 in 12%) and DVT in the Thal-Dex arm (15% of all cases including 26% in the first 19 patients which decreased to 12% among the rest who were treated with warfarin). The mortality rate was similar in both groups at 6%. In both treatment arms the yield of stem cells and the number of aphereses required to collect adequate stem cells were the same.

In the present study, Barlogie et al used three different regimens, all containing high dose dexamethasone, as part of the induction, probably with the aim of achieving maximal tumour reduction before transplant. Whether this approach had better responses compared to use of one regimen for 3-4 months will not be known as the response rates after each phase of therapy has not been reported in this study. To reduce the risk of relapse, they studied the role of maintenance therapy following high-dose therapy (HDT). The IFM 99-02 study earlier evaluated the effect of thalidomide maintenance treatment on the duration of response after

high-dose therapy and ASCT, as well as the effects of pamidronate on the incidence of bone events after high-dose therapy. 780 patients, < 65 years, received 3-4 cycles of VAD, a first ASCT with melphalan 140mg/m², and a second ASCT with melphalan 200mg/m². Patients without progressive disease 2 months after the second ASCT were randomized to receive no maintenance treatment (arm A), maintenance treatment with pamidronate (arm B) or maintenance treatment with thalidomide and pamidronate (arm C). Maintenance therapy with thalidomide improved the CR rate the duration of response, and OS. The 4-year EFS was 50% in the thalidomide/pamidronate maintenance arm and 4-year overall survival was 87%, which were both significant.³ This is the first study to show improvement in overall survival with single agent thalidomide as maintenance. The optimal dose of thalidomide has not been established. In present study the dose of thalidomide used was different in various phases of therapy.¹

The lack of significant survival benefit in this study has been partly attributed to the shorter survival in the thalidomide arm after relapse (1.1 vs 2.7 years). After relapse, 75% of patients on the thalidomide arm continued to receive thalidomide, probably at higher doses. Whether use of drugs other than thalidomide in this arm would have led to different outcomes remains speculative. On intent to treat basis, the overall survival of patients in the thalidomide arm was not significantly different from the control arm. However the EFS and OS were significantly longer in patients who had a CR compared to those who had partial or no response. Also patients who achieved complete responses after transplantation had better EFS and OS than those who did not achieve the same.¹ The benefit of melphalan based tandem transplants was most evident in the group of patients who had not achieved CR after the first transplant. On the contrary, the study by Rajkumar et al, showed that achieving a CR after transplantation does not lead to better EFS and OS.⁴ Similarly, except in the IM 99-02 study, there is no other study where maintenance thalidomide has been shown to improve overall survival.³ This is in spite of maintenance thalidomide resulting in more complete

responses. In the light of these conflicting results the value of CR as a surrogate for overall survival needs to be evaluated further.

Thalidomide is associated with a variety of side effects. Sedation, constipation and peripheral neuropathy are cardinal toxicities. Skin reactions are a common side effect and may develop in upto 46% of patients. The reactions may range from a non pruritic rash to erythema multiforme and Steven Johnson syndrome .

Other side effects include-peripheral edema, xerostomia, hypothyroidism, tremors and bradycardia. In this study,¹ the incidence of symptomatic sinus bradycardia was higher, 12% and one third of them had a pacemaker implanted. The phase of the study during which this complication occurred and the possible reasons for this higher than reported incidence has not been discussed.

Deep vein thrombosis (DVT) is another serious complication of this drug. Here the incidence of DVT was 34% in the first 162 patients.¹ The exact cause for DVT is unknown. Early 'in vitro' data suggest that thalidomide may be procoagulant and proangiogenic through stimulation of thrombin receptors of doxorubicin-injured endothelium.⁵ Other studies have shown that within 4 weeks of thalidomide therapy, there is significant elevation of factor VIII coagulant activity and of von willerbrand factor antigen in patients with active myeloma or other cancers.⁶ The major risk for DVT occurs in early disease when the tumour load is maximal and with addition of dexamethasone or chemotherapy especially doxorubicin. Aspirin or low-dose warfarin prophylaxis are ineffective. Therapeutic anticoagulation with warfarin (INR, 2 to 3) or low-molecular-weight heparin can abrogate the excess risk of DVT.⁷ Thalidomide-based regimens can be safely resumed in patients with DVT once therapeutic anticoagulation has been established. The incidence of DVT may be reduced by using lower doses of thalidomide (50-100mg), delaying thalidomide until the 3rd month unless patient is highly symptomatic, avoiding usage of erythropoietin which is a procoagulant, early in the course of disease and lowering the doses of steroids.⁸

In conclusion, the addition of thalidomide into high dose therapy for myeloma increased

the frequency of complete responses and extended event free survival at the expense of more adverse effects. The overall survival was not improved. Newer novel agents have shown better response rates upfront with lesser toxicity. However, the durability of these responses remains to be proved. More agents are required for salvage therapies in patients who progress while on thalidomide.

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