Multiple Myeloma

Combination chemotherapy with cyclophosphamide, thalidomide and dexamethasone for patients with refractory, newly diagnosed or relapsed myeloma

We evaluated the combination of thalidomide, pulsed dexamethasone and weekly cyclophosphamide (CTD) for the treatment of patients with newly diagnosed, relapsed or VAD-refractory multiple myeloma. We found that this combination was highly effective in inducing responses in all treatment groups with an overall response rate of 83.8%. CTD was well tolerated and did not impair stem cell mobilization.

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Regimens containing high dose steroids combined with vincristine, adriamycin±cyclophosphamide (VAD, VAMP, C-VAD) have been widely used for first line treatment for younger patients with multiple myeloma. The overall response rate to these combinations is 55-75% with complete response (CR) rates up to 24%.[1] Patients refractory to these regimens have a poor prognosis and short survival. Although high dose therapy may improve survival in this group,[2] it is also known that the outcome following stem cell transplantation (SCT) is superior for patients who have responded to induction therapy,[3] suggesting that the aim should be to maximize the efficacy of induction treatment. In view of recent data demonstrating a high response rate to thalidomide-based regimens in myeloma[4,5] we evaluated the efficacy of combining low dose thalidomide with cyclophosphamide and pulsed dexamethasone (CTD).

Since 2001 we have treated 62 patients with stage II/III myeloma (median age 60 years, range 31-73 years) with CTD, comprising a 4-week cycle of oral cyclophosphamide 500 mg on days 1, 8 and 15; thalidomide 100 mg daily initially, increasing to 200 mg daily if tolerated; and oral dexamethasone 40 mg daily on days 1-4 and 15-18 of each cycle. No anticoagulants or anti-platelet agents were used. Patients were treated with two to six cycles of CTD depending on tolerance and response. Following CTD therapy, all eligible patients achieving a partial response (PR) or better underwent stem cell mobilization, followed by high dose melphalan and peripheral blood SCT. The patients initially targeted were those with VAD-refractory disease (n=29) having had <50% reduction in their paraprotein after three cycles or <25% reduction after two cycles of VAD/C-VAD, and those who had relapsed following VAD/C-VAD (n=16) or oral chemotherapy (n=2), of whom 16 had previously been transplanted (14 autologous and 2 allogeneic transplants). Fifteen newly diagnosed patients were also treated.

There was little regimen-related toxicity: grade 1-2 constipation occurred in 16%, somnolence in 6.5% and parasthesia in 9.7%. Thalidomide was stopped in two patients due to peripheral neuropathy and dose reductions were required in a further five patients. The only grade 3 toxicities were deep vein thrombosis in two patients (3.2%) and febrile neutropenia in three patients (4.8%). Using EBMT response criteria,[6] 52 patients (83.8%) achieved a PR or better (Table 1). Thirteen (21%) achieved a very good partial response (VGPR), six patients a minor response (MR) and only four patients (6.5%) failed to respond. Of the VAD-refractory patients 25/29 (86%) achieved a PR or better and one had a MR, leaving only three of these patients (10%) refractory to CTD. Fourteen of the 18 relapsed patients (78%) achieved at least a PR, three had a MR and one patient was refractory. In the untreated group, 4/15 achieved a VGPR (26.7%) and 11 (60%) a PR.

Table 1. **Responses to CTD therapy (by disease status and overall).**

Response (% fall in paraprotein)	*Refractory group n=29* *n*	*Relapsed group n=18* *n*	*De novo group n=15* *n*	*Overall n=62* *n (%)*
≥90%	3	6	4	13 (20.9%)
50-90%	22	8	9	39 (62.9%)
25-50%	1	3	2	6 (9.7%)
<25%	3	1	0	4 (6.5%)

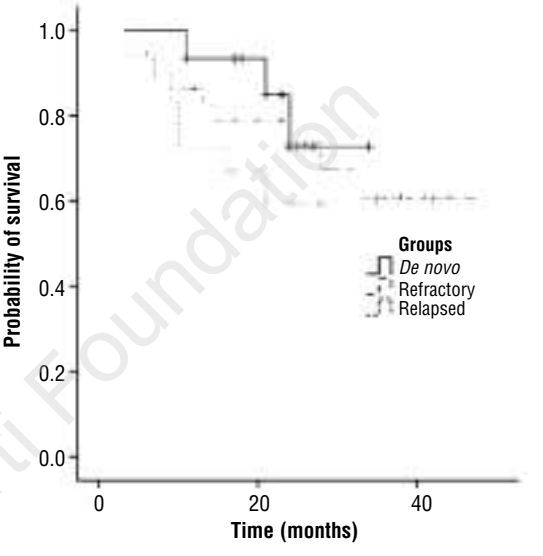

Figure 1. **Kaplan-Meier estimate of overall survival from start of CTD treatment (by group).**

Successful stem cell mobilization was achieved in 39/43 patients with a median of 4.71×10^6 $CD34^+$ cells/kg harvested (range 1.81–17.4). Mobilization failed in four patients and was not attempted in the remaining 18 patients due to advanced age, progressive disease, availability of a matched donor or previously harvested stem cells.

Forty patients went on to receive high dose therapy leading to CR in 13 patients (37%). Of these SCT procedures 13 were performed in previously untreated patients and 25 in those with refractory disease of whom four had achieved CR (16%). Only two out of five relapsed patients had successful harvests and went on to a second SCT whilst the others received alternative maintenance therapy. With a median follow up of 24 months (range 3-47) the overall survival rate among all patients was 69.8% and none of the 19 deaths was treatment related.

In the relapsed group 11/18 remain alive at a median follow up of 20 months (Figure 1).

In summary the CTD regimen is well tolerated and proved highly effective in all three groups of patients studied. No CR were observed but this may have been due to rapid stem cell mobilization and SCT immediately a PR was achieved. The observed overall response rate of 83.8% compares favorably with that reported for VAD/C-VAD. Furthermore, confirming other studies,[7-10] the combination of CTD appears to be superior to thalidomide alone or combined with dexamethasone, although it is difficult to compare results accurately. Importantly, CTD was effective in patients who had failed to respond to VAD/C-VAD therapy with 85% of this group achieving a PR. This group has an adverse prognosis although they may benefit from high dose therapy. Since response to induction therapy is correlated with survival following SCT,[3] the use of CTD to improve responses to induction therapy in newly diagnosed patients, or switching VAD refractory patients to CTD to maximize their response, may lead to improved survival.

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