Thalidomide plus Monthly High-dose Dexamethasone in Chemorefractory Myeloma. Results of a Phase II Clinical Study

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Abstract. Thalidomide is a potent anti-myeloma drug which can produce up to a 30-50% overall response rate (ORR) in pre-treated, chemorefractory multiple myeloma. Most authors agree with using 200 mg/daily with associated high dose dexamethasone (40 mg/daily x 4 days, 3 times monthly) considering lower doses investigational. We report our experience using thalidomide 100 mg/daily plus dexamethasone 40 mg/daily once a month, in 27 pre-treated patients. Thalidomide dose escalation and/or association with other drugs were established on the basis of the patient’s response. Median age was 69 years (range 50-83 years) and 16 male and 11 female patients were treated. All patients had received more than 1 treatment line (range 1-5). Thalidomide was increased up to 300 mg/daily in 10 patients and 1 patient received up to 400 mg/daily. Two patients were not evaluable because of early death, 1 did not tolerate thalidomide because of pulmonary and neurological side-effects. Sixteen patients responded to this treatment, with an ORR of 66%. The combination of low-dose thalidomide plus monthly high-dose dexamethasone in chemorefractory myeloma showed interesting palliative results. According to our data, increasing thalidomide dosage and/or adding further drugs does not generally produce significant improvement.

Thalidomide has been included in the management of myeloma since the publication of Sighal et al. in 1999, in which up to 32% of the 84 pre-treated multiple myeloma patients responded to thalidomide, given at 200 to 800 mg/daily (1). In a recent paper, the overall response rate (ORR) of 63% by giving thalidomide 200 mg/daily plus dexamethasone 40 mg/daily on days 1 to 4, 9 to 12 and 17 to 20, in 207 previously untreated patients was reported (2). These dosages are now generally considered a standard by most authors (3).

We report our experience and an update of our open phase II study (4). We have enrolled 27 previously treated multiple myeloma patients who received low-dose thalidomide and low-dose dexamethasone, obtaining results confirming literature data but with lower toxicity.

Materials and Methods

Twenty-seven patients were enrolled in the study, 16 male and 11 female. Median age was 69 years (range 50-83 years). All had received at least one line of treatment (range 1-5), mostly melphalan and prednisone as first line. The other up-front treatments received were: VAD (vincristine, Adriamycin, dexamethasone; 14 patients), radiation therapy (5 patients), Endoxan (4 patients), alpha-interferon (2 patients) and high-dose melphalan with autologous stem cell transplantation (1 patient).

All patients gave their informed written consent. Treatment consisted of thalidomide 100 mg administered at night and 40 mg oral dexamethasone given for 4 days each month. Baseline electroneurography plus monthly controls were performed during the therapy. All patients received zolendronic acid every month. Erythropoietin was given to maintain haemoglobin levels above 8 g/dl.

Three patients were not evaluable, two because of early death and one because of premature treatment interruption due to severe side-effects; one had 68.5% monoclonal component reduction after 4 weeks before developing neurological complication and renal failure.

Results

In 16 patients serum or urinary monoclonal component concentration decreased with a median of 51% (range 12-90%). In one patient there was a loss of secretary capacity, but she had bone pain reduction and haemoglobin concentration increase. In another patient, increasing

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thalidomide dosage from 100 to 200 mg produced a decrease of urinary light chain excretion from original 82.5 to 97%. The patient had to stop the drug because of neuropathy. She had a stable disease for 93 months, continuing to take dexamethasone and alpha-interferon. In another patient, increasing the dose of thalidomide to 200, 300 and 400 mg resulted in a reduction of monoclonal protein. We noted, in another patient in which thalidomide was given at 100 mg, a reduction of 90% which lasted 4 months, after which increasing to 200, 300 mg and adding Endoxan 100 mg daily, twice a week for two weeks, induced a clear further response. One of our patients received bortezomib 1.3 mg/m² at progression and this resulted in a complete remission.

Side-effects were observed in nine patients. In three patients death was probably related to thalidomide (one acute renal failure, one cerebral venous sinus thrombosis and one pulmonary hypertension). In two patients mental confusion occurred with one consequent early treatment stop and one dose-reduction.

Two patients stopped therapy because of G3 neuropathy: in one an asymptomatic sinus brachicardia was observed without thalidomide dose modification and in one patient thalidomide was momentarily stopped because of cerebral ischemia after which the patient resumed thalidomide without further side-effects while taking aspirin.

Discussion

We report an ORR of 66% and a median overall survival of 37 months.

Our data confirm that lower doses of thalidomide and dexamethasone may induce the same results as greater dosages, with lower and fewer side-effects.

This experience seems to reinforce the view that the magnitude of response to therapy is not prognostically significant (5) in pre-treated patients.

The significant reduction of monoclonal component concentration obtained with thalidomide and dexamethasone, was followed by disease progression in 4 months.

Generally, neither thalidomide dosage increase, nor addition of further drugs influenced the outcome.

Two patients, after 47.6% and 48% reduction, are still in good health, one taking 100 mg thalidomide on alternate day (52 months), the other taking alpha-interferon and monthly dexamethasone after the development of neurological toxicity (18 months).

Thalidomide has two novel exciting applications: first, as up-front therapy in association with melphalan and prednisone (MPT), where it induces a response rate similar to autologous bone marrow transplantation (6). Second, it can be used as a debulking treatment before high-dose therapy, showing less toxicity and comparable CD34+ harvesting (7).

In relapsed patients, thalidomide should be used at the lowest effective dose (100 mg/daily) in association with a single monthly high-dose of dexamethasone (40 mg). According to our data, increasing thalidomide dosage and/or adding further drugs, does not generally produce significant disease improvement.

References


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