Long-term Control in a Patient with Refractory Multiple Myeloma by Oral Cyclophosphamide and Dexamethasone

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Abstract. *Background: Prognosis of patients with multiple myeloma (MM) has substantially improved in recent years due to the incorporation of novel drugs into their treatment. However, older drugs should be kept in mind when modern drugs have failed. Case Report: We report on a 62-year-old female patient with high-risk, refractory light-chain myeloma who initially presented with acute renal failure and was consecutively treated with six different therapies without achievement of sustained disease control. Therapy of cyclophosphamide orally at 50 mg/day (100 mg twice a week) and dexamethasone at 24 mg once weekly was initiated, resulting in a very good partial response which was maintained for more than 21 months. Low-dose cyclophosphamide in combination with dexamethasone was well-tolerated and no significant hematological or nonhematological side-effects were noted. Conclusion: We suggest that older drugs should be kept in mind as treatment options for patients with disease refractory to multiple therapies, including novel agents.*

Multiple myeloma is a disease characterized by the proliferation of malignant plasma cells, resulting to an increased concentration of monoclonal paraprotein in serum, urine, and in the case of secondary amyloidosis, tissues. Classically, the clinical hallmarks of multiple myeloma include hypercalcemia, renal failure, anemia, bone lesions, infections, hyperviscosity and secondary neuropathies. The clinical importance of multiple myeloma is evidenced by the fact that it accounts for 10% of all hematological malignancies and the 5-year relative survival rate is about 47% (1). Treatment for younger patients should consist of novel agent (thalidomide, lenalidomide, bortezomib)-based two- or three-drug combinations followed by high-dose melphalan and autologous stem cell transplantation (ASCT). For non-transplant candidates, the combination of bortezomib, melphalan, prednisone or lenalidomide and dexamethasone are valuable options. Unfortunately, an overwhelming majority of patients suffer relapses of their disease and, if they become symptomatic, further treatment is necessary. Tumor response can be achieved in an ever shrinking proportion of patients with each relapse and treatment-free intervals and progression-free survival tend to shorten with each treatment line (2). Optionally, one way to overcome resistance in patients who suffer from advanced myeloma is to treat with an older drug, such as cyclophosphamide (3).

Herein, we report on a 62-year-old female patient with refractory light-chain myeloma in whom we achieved long-standing disease control with cyclophosphamide orally at 50 mg/day (twice a week 100 mg) combined with dexamethasone at 24 mg orally once weekly. Moreover, this regime has the possibility of oral application and is cost-effective.

Case Report

A 62-year-old hitherto healthy woman was admitted to our hospital in May 2009 due to acute renal failure with a serum creatinine level of 7.9 mg/dl (normal range=0.51-0.95 mg/dl).

A diagnostic work-up revealed light-chain myeloma with free light-chain-κ (FLC-κ) in serum of 10,900 mg/l (normal range=3.3-19.4 mg/l) as underlying disease. She was slightly anemic with a hemoglobin value of 9.5 g/dl (normal range=12.0-15.7 g/dl). There was no hypercalcemia. Evaluation of the bone marrow revealed 64% plasma cells characterized by del13q, t(11;14), and a immunoglobulin heavy-chain (IGH) rearrangement (complex karyotype). X-Ray examinations showed multiple small lytic bone lesions in the skull and axial skeleton.

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Induction therapy was immediately initiated with intravenous bortezomib (Velcade® at 1.3 mg/m^2 days 1, 4, 8, 11) and oral dexamethasone (40 mg, days 1-4 and 9-12) administered for two 21-day cycles (VD), accompanied by hemodialysis using a high-cut off membrane (HCO 1100). After two treatment cycles, regression of serum creatinine to 3.34 mg/dl and FLC-κ to 4,090 mg/l, respectively, occurred and thalidomide at 100 mg was added to the treatment for a further three cycles, resulting in very good partial response (VGPR) according to International Myeloma Working Group criteria (4). After harvesting peripheral blood stem cells using granulocyte-colony stimulating factor priming, maintenance treatment with low-dose lenalidomide at 5 mg per day continually was given over two years because of the refused high dose melphalan therapy at that time.

On disease progression (creatinine increased from 2.3 mg/dl to 3.7 mg/dl, FLC-κ to 9,520 mg/l, and hemoglobin decreased from 10.4 g/dl to 8.3 g/dl), we reinitiated bortezomib/dexamethasone. Due to further increasing FLC-κ after one treatment cycle, we added bendamustine (100 mg/m^2 on days 1 and 2) (5), without any clinical or biochemical response. Consequently, the patient received high-dose melphalan (100 mg/m^2) followed by ASCT. FLC-κ dropped from 24,220 mg/l to a minimum of 1,120 mg/l three months after ASCT and maintenance with low-dose lenalidomide was begun (5 mg continually for four months; the creatinine level in this period ranged between 3.14 mg/dl and 3.28 mg/dl) until the FLC-κ again increased to 3,490 mg/l. The dose of lenalidomide was escalated to 15 mg daily in combination with dexamethasone at 24 mg twice per week. On further progression, seven months after ASCT, we started a combination of bortezomib, pegylated liposomal doxorubicin (30 mg/m^2 on day 4) (6) and dexamethasone. However, the disease progressed again within a short period of time (Figure 1) and thus we ultimately prescribed cyclophosphamide orally at 50 mg/day (twice a week 100 mg) combined with dexamethasone at 24 mg orally once weekly, resulting in a VGPR which was maintained for more than 21 months without any evidence of disease progression.

Laboratory tests recently impressed with a serum creatinine level of 1.88 mg/dl and a concentration of FLC-κ in serum of 1.470 mg/l. The radiological findings showed no progression of the pre-existing bone disease, which was treated with intravenous ibandronic acid. Continuous oral cyclophosphamide in combination with dexamethasone was well tolerated and no significant hematological or non-hematological side-effects were noted.

Discussion

The common approach to treating progressive disease in relapsed/refractory MM is the use of sequential combination regimens designed to control the disease with the best quality of life for as long as possible. Fortunately, the number of options available for both frontline and relapsed/refractory settings has increased through the combination of dexamethasone with new drugs such as bortezomib with/without thalidomide or lenalidomide. When combining new drugs with melphalan, bendamustine, pegylated liposomal doxorubicin or cyclophosphamide, high response rates and prolonged remissions have been reported even in patients with advanced myeloma (7). Our patient had MM refractory to multiple treatments, including novel drugs, and ultimately received a convenient combination of oral cyclophosphamide at 50 mg per day (twice a week 100 mg) and dexamethasone at 24 mg once weekly, resulting in the achievement of a VGPR which was maintained for more than 21 months without any toxicity.

Trieu *et al*. reported that weekly applications of cyclophosphamide (500 mg) and alternate day prednisone (100 mg) in 59 pre-treated patients resulted in an overall response rate of 61%, with 41% partial remissions. This regimen was well-tolerated, with myelosuppression responsive to dose reduction noted in only 11% of patients (8). Weekly oral cyclophosphamide plus dexamethasone is effective in the setting of relapsed disease, and represented one arm of the first-line therapy in the Medical Research Council Myeloma IX trial (9). Fan Zhou *et al*. recently published the results of a prospective trial using low-dose cyclophosphamide (50 mg/day) and prednisone (15 mg/day continually) in 56 patients with relapsed/refractory MM and severe cardiac insufficiency. An overall clinical benefit was notified in 63.0% (complete remission=3.7%; VGPR=7.4%; partial remission=48.1%; stable disease=3.7%), with a median survival of 8 months (range=1-70 months), indicating that this regimen is effective even in patients with substantial co-morbidity (10).

Moreover, this treatment regimen represents an attractive base for the addition of other agents. The addition of cyclophosphamide to thalidomide and dexamethasone (11), to lenalidomide and dexamethasone (12), and to bortezomib and dexamethasone (13) has been shown to increase response rates and possibly prolong survival of patients with refractory/relapsed MM. Thus, the addition of cyclophosphamide may enhance the therapeutic efficacy of novel agents. Features of metronomic chemotherapy (14), *i.e*. the application of relatively low doses of treatment over a prolonged period of time, which is intended to target not only tumor cells but also their microenvironment, *i.e*. inhibiting tumor angiogenesis, might play a role in the unexpected efficacy of this regimen in heavily pre-treated patients with myeloma.

In summary, our case reported here indicates that the combination of low-dose cyclophosphamide with dexamethasone is an effective, safe and inexpensive treatment option in heavily pre-treated patients with multiple myeloma and should be kept in mind when modern drugs have failed. Moreover, this therapy is an attractive low-cost low-risk therapeutic option, especially in healthcare markets where high-cost second-generation drugs (*e.g*. pomalidomide, and carfilzomib) are not available or have already been applied.

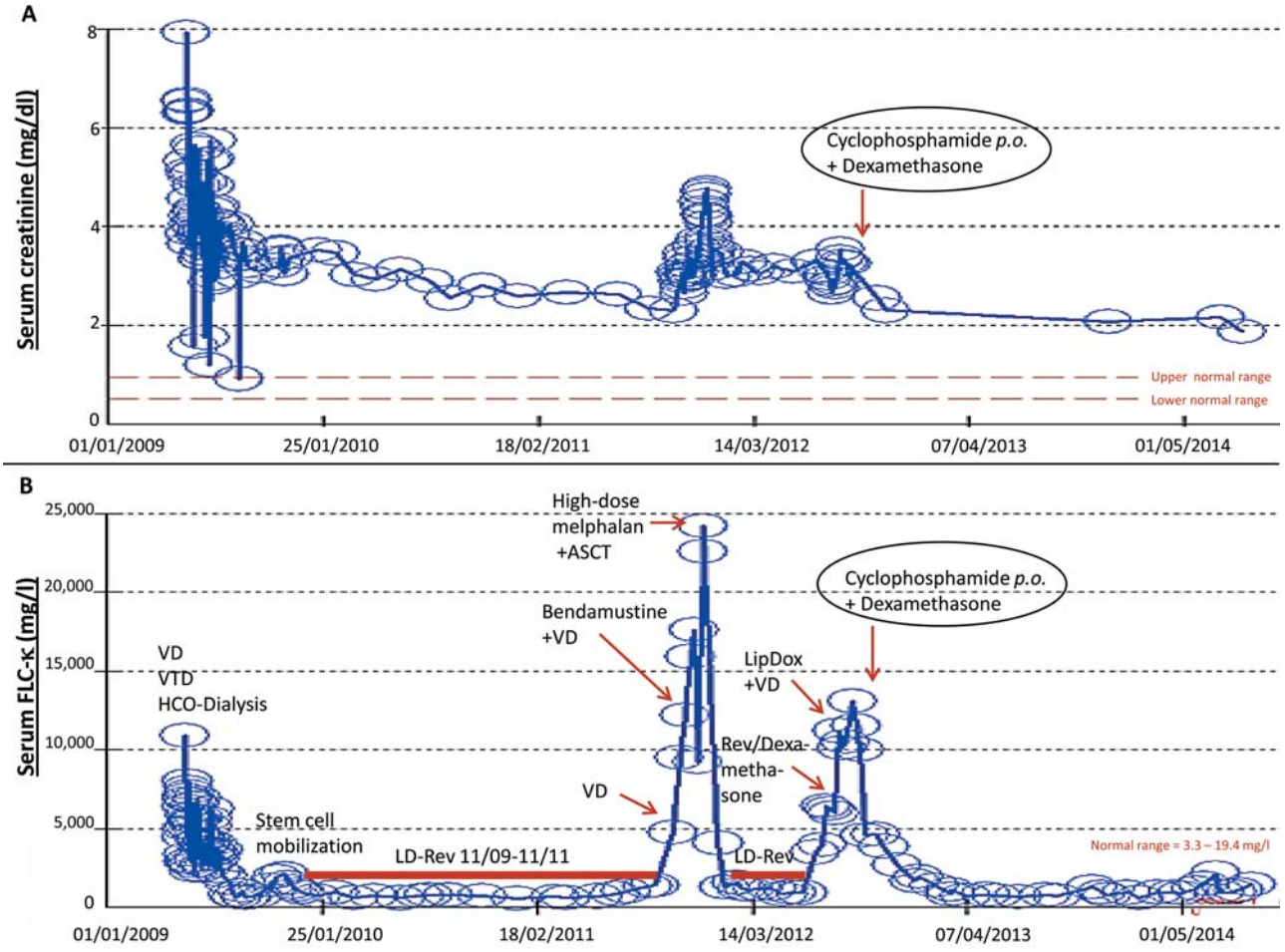

Figure 1. *A: The course of serum creatinine and initiation of cyclophosphamide and dexamethasone. B: The course of serum free light-chain-κ (FLC-κ) during multiple therapy regimens, with cyclophosphamide and dexamethasone. HCO: High-cut off membrane; VD: bortezomib/dexamethasone; VTD: bortezomib/thalidomid/dexamethasone; LD-Rev: low-dose Revlimide; Rev: Revlimide; LipDox: liposomal doxorubicin; p.o.: per os.*

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