Combination Therapy with Thalidomide, Incadronate, and Dexamethasone for Relapsed or Refractory Multiple Myeloma

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Abstract

The feasibility and efficacy of a combination of thalidomide, incadronate, and dexamethasone (TID) were studied in 12 patients with relapsed or refractory multiple myeloma. The protocol, consisting of 300 mg/day of thalidomide administered orally, intravenous incadronate (10 mg/day) administered weekly, and 12 mg/day dexamethasone for 4 days, was repeated every 3 weeks. Evaluations of efficacy and toxicity were carried out every 3 weeks and were continued for 3 cycles. Three patients were excluded during the study because of apnea, severe somnolence, and pancytopenia. Of 9 evaluated patients, the partial responses achieved in 3 patients and the minor responses achieved in 4 patients corresponded to a response rate of 78% according to the criteria of the European Group for Blood and Marrow Transplantation. In addition, painful osteolytic symptoms improved rapidly after 1 cycle of TID therapy in the 10 patients evaluated. These data suggest that TID is a feasible and promising therapeutic approach for refractory and relapsed multiple myeloma.

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Key words: Multiple myeloma; Thalidomide; Incadronate; Dexamethasone

1. Introduction

Multiple myeloma (MM) is a malignancy of B-cells characterized by the monoclonal proliferation of malignant plasma cells and osteolytic bone destruction. Several chemotherapeutic regimens for MM have been developed, and only high-dose melphalan supported by autologous stem cell transplantation (auto-SCT) has improved the survival prospects of patients with MM [1-3]. However, many patients were found to relapse during a long-term follow-up period after auto-SCT [1-3]. Allogeneic SCT (allo-SCT) is possibly the only curative therapy for MM. A graft-versus-myeloma effect by immunocompetent donor lymphocytes has been demonstrated, but the treatment-related mortality rate is high [4,5]. Nonmyeloablative SCT has recently been reported to provide stable engraftment of allogeneic stem cells and tolerable toxicity in patients with MM, but a longer follow-up period is necessary to evaluate late mortality [6-8]. Therefore, there is an obvious need for new therapeutic strategies.

Thalidomide has proved to be a useful drug for the treatment of refractory and relapsed MM patients, and efficacies of up to 35% have been reported in several clinical trials [9-11]. The antitumor mechanisms of thalidomide in MM are complex, and the possible mechanisms include inhibition of angiogenesis and myeloma cell adhesion to stromal cells, modulation of several cytokines, and stimulation of the immunoreaction of CD8+ T-cells to myeloma cells [12,13]. Moreover, thalidomide has been reported to restore the sensitivity of myeloma cells to other drugs and to enhance the antmyeloma activity of dexamethasone [14]. The combination of thalidomide with dexamethasone or combination chemotherapy including dexamethasone has been reported to be more effective than treatment with thalidomide alone or combination chemotherapy without thalidomide [15-21].

Bisphosphonates such as pamidronate have reduced the incidence of skeletal events and have improved the quality of life of MM patients. They are now one of the most important classes of drugs for the treatment of bone disease in MM [22,23]. The inhibition of osteoclasts by a bisphosphonate disrupts the relationship between osteoclasts and MM cells, thereby providing a less favorable environment for the MM cells to grow and indirectly modulating tumor growth [24].
Moreover, some reports have demonstrated that nitrogen-containing bisphosphonates such as incadronate have direct antmyeloma effects through the inhibition of the mevalonate pathway and the prevention of posttranslational prenylation of guanosine triphosphate–binding proteins, including Ras [24-27]. Ras gene activation frequently ranges from 30% to 40% in MM, and point mutations frequently occur in this gene [26]. On the basis of these observations, we investigated the effect of the combination of thalidomide with incadronate and dexamethasone (TID therapy) in a clinical phase 2 trial for relapsed or refractory MM patients to assess its efficacy and toxicity.

2. Patients and Methods

2.1. Patients

Between April 2001 and December 2003, 12 patients were treated with the combination of TID therapy after informed consent was obtained from each patient. The diagnosis of MM was made according to standard definitions [28]. Criteria for inclusion also included a life expectancy greater than 1 month and the absence of irreversible organ deterioration. Exclusion criteria were as follows: (1) the existence of a myelodysplastic syndrome or other hematologic malignancies different from MM; (2) the presence of clinical neurologic abnormalities or dementia; (3) the presence of clinical liver dysfunction, uncontrolled infection, uncontrolled hypercalcemia, or pregnancy; (4) the presence of unrecoverable cytopenias (<0.5 × 10⁹/L granulocytes); or (5) the presence of uncontrolled diabetes mellitus.

2.2. Therapeutic Protocol

The protocol was approved by the institutional review board at Kyoto Prefectural University of Medicine. Thalidomide (Talizer) was supplied in 100-mg tablets by Serral (Mexico City, Mexico) and was administered nightly. Patients were initially given 100 mg thalidomide daily, and TID therapy was started a week later. The regimen consisted of 300 mg/day of orally administered thalidomide, 10 mg/day incadronate administered intravenously on days 1, 8, and 15, and 12 mg/day dexamethasone administered on days 1 through 4 (Figure 1). This regimen was performed 3 times in each patient. The dose of thalidomide was reduced by 100 mg/day if nonhematologic toxicity due to thalidomide (except constipation and skin rash) of grade ≥2 developed or if hematologic toxicity of grade ≥3 developed. Treatment was stopped according to National Cancer Institute (NCI) Common Toxicity Criteria version 2 in cases of nonhematologic toxicity of grade ≥3 or hematologic toxicity of grade 4 due to TID therapy. Any patient who developed grade 2 constipation was administered a laxative. After 3 cycles of TID therapy, patients received maintenance therapy consisting of thalidomide (50-100 mg/day), dexamethasone (2-8 mg/day for 4 days every 4 weeks), and incadronate (10 mg every 4 weeks) according to their condition until disease progression.

2.3. Evaluation

All patients had baseline evaluations that included physical examinations, blood counts, liver and renal function tests, bone marrow aspirations, serum and urine protein electrophoresis analyses, measurements of serum immunoglobulin, and serum lactate dehydrogenase and β₂-microglobulin analyses. Chest radiography and bone surveys were also performed. Evaluations for bone lesions were carried out by using a bone scale proposed by Durie and Salmon [29]. Bone pain was evaluated according to the NCI Common Toxicity Criteria (version 2).

2.4. Assessment of Response and Toxicity

The primary end point of this study was to demonstrate the toxicity and feasibility of TID therapy. All patients who received TID therapy were eligible for assessment of toxicity. The efficacy and toxicity of TID therapy were evaluated every 3 weeks, and these evaluations continued for 3 treatment cycles. Response was assessed according to the criteria of the European Group for Blood and Marrow Transplantation [30]. An assessment of complete response (CR) required both the disappearance of serum or urine monoclonal paraprotein as determined by immunofixation techniques and <5% bone marrow plasma cells. Partial response (PR) was defined as a reduction of 50% or more in the serum monoclonal paraprotein level or a reduction in the urinary excretion of light chain over 24 hours of >90% or to <200 mg, and a >50% decrease in the size of soft-tissue plasmacytomas. Minimal response (MR) was defined as a reduction in the serum monoclonal paraprotein level by 25% to 49%, by a reduction in the urinary excretion of light chain over 24 hours of >50% to 89%, or by a decrease of 25% to 49% in the size of soft-tissue plasmacytomas. The response rate including CR, PR, and MR was evaluated for all patients who completed 3 cycles of TID therapy. The NCI Common Toxicity Criteria (version 2) were used to grade adverse effects.