Thalidomide as a Targeted Therapy for Multiple Myeloma

Key words: multiple myeloma, thalidomide, immunomodulatory analogues, angiogenesis

Multiple myeloma is a highly malignant hematological disease and is hardly cured with conventional chemotherapy. Although high-dose chemotherapy with autologous stem cell transplantation increases the complete remission rate and improves event free survival and over all survival (1, 2), there is no plateau of the survival curves and many patients still relapse (3, 4). Therefore several strategies concerning the methods of transplantation, such as the conditioning regimen, number of transplantations, source of stem cells and allogeneic transplantation, are under investigation to improve the treatment results.

Many malignant neoplasms such as breast, prostate and non small cell lung cancers are dependent on neovascularization to sustain growth. Recently increased blood vessel formation (angiogenesis) in the bone marrow of the patients with multiple myeloma was reported (5) and elevated levels of several angiogenic cytokines in patients with myeloma was also reported (6). In 1994, D’Amato et al (7) reported that orally administered thalidomide was an inhibitor of angiogenesis induced by basic fibroblast growth factor in a rabbit cornea micropocket assay. Thalidomide was developed as a sedative but was proven to be a potent teratogen seen in babies with limb defects in association with maternal thalidomide usage. They revealed that the limb defects seen with thalidomide were secondary to an inhibition of blood vessel growth in the developing fetal limb bud caused by the antiangiogenic activity of thalidomide. From these considerations, Singhal et al (8) performed a clinical trial of thalidomide as a single agent in patients with advanced and refractory myeloma. The overall response rate was 32% which was associated with a decreased number of plasma cells in bone marrow and increased hemoglobin levels. After a median follow-up of 14.5 months, the median time to progression had not been reached. Considering that these patients had relapsed after chemotherapy, 90% with a relapse after high-dose chemotherapy, these effects of thalidomide is magnificent. On the other hand, many patients suffered from troublesome side effects such as weakness, fatigue, somnolence, neuropathy and constipation especially at the higher dose of thalidomide. Also it is unclear whether there is a dose-response relationship with its effectiveness. Therefore, it is necessary to determine the optimal dose of thalidomide and the schedule of administration. In this issue, Hayashi et al (9) reported a patient with IgD myeloma and renal failure requiring chronic hemodialysis who responded to thalidomide. IgD multiple myeloma is often accompanied by renal failure and shows poor prognosis. The authors revealed that thalidomide treatment is also effective for IgD myeloma as it is for other types of myelomas. Concerning the thalidomide therapy against myeloma with renal failure, especially in chronic hemodialysis, there is no report yet. This is the first report on thalidomide therapy in a patient receiving chronic hemodialysis.

Thalidomide has been shown to inhibit angiogenesis induced by fibroblast growth factor (7). Nevertheless, Singhal et al (8) found no correlation between the microvascular density of bone marrow and the response to thalidomide. These findings suggest that other mechanisms may work in addition to inhibition of angiogenesis in the usage of thalidomide for multiple myeloma. Thalidomide is known to have a broad spectrum of pharmacologic and immunologic effects (10). Thalidomide directly induces either apoptosis or G1 growth arrest in myeloma cells and enhances the anti-myeloma activity of dexamethasone (11). Vascular endothelial growth factor and interleukin-6 secretion are significantly increased in cultures of multiple myeloma cells adherent to bone marrow stromal cells and thalidomide abrogates the adhesion-related upregulation of both vascular endothelial growth factor and interleukin-6 (12). Myeloma patients treated with thalidomide show an increase in interleukin-2 and interferon-γ secretion, which augments NK cell number and function (13).

Recently more potent and less toxic thalidomide derivatives have been sought due to the significant dose-limiting side effects of thalidomide, including weakness, fatigue, somnolence, neuropathy and constipation. CC-5013 (REVIMID) is a thalidomide analogue which is 50 to 2,000 times more potent than thalidomide in its immunomodulatory activity. A phase I dose-escalation study in 27 patients with relapsed and refractory myeloma was carried out (14). These patients were heavily treated including previous thalidomide therapy. At least a 25% reduction in paraprotein occurred in 71% of the patients, including 46% of the patients who had received prior thalidomide. Importantly, no significant somnolence, constipation or neuropathy was seen in any cohort. A phase II trial of CC-5013 is now ongoing in USA. A large searching for a wide variety of novel agents targeting multiple myeloma cells and their bone marrow micro-
environment has been carried out and one of these promising agents is proteasome inhibitor, PS-341 (15). These novel therapies including thalidomide, its immunomodulatory analogs and proteasome inhibitor in patients with refractory and relapsed multiple myeloma provide a new paradigm targeting the myeloma cells and bone marrow microenvironment.

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References