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Introduction

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Thalidomide represents a new milestone in the treatment of multiple myeloma and an opportunity to move away from cytotoxic agents toward an approach based on cellular signaling and cell-cell interactions. Alone, thalidomide produces several immunomodulatory effects that retard the progression of disease. In combination with conventional treatments, however, thalidomide produces a significant synergistic effect, resulting in improved treatment response and survival rates.

The mechanism of action of thalidomide is complex. It impedes angiogenesis, alters myeloma plasma cell adhesion, increases the number of natural killer cells, and stimulates T-cell proliferation. Thalidomide also appears to produce direct anti-myeloma activity *in vitro*. The effect of thalidomide on T cells is of particular interest because the presence of $CD8^+$ T-cell clones is associated with a favorable prognosis, and such clones are stimulated by thalidomide. The effect of thalidomide on fibroblast growth factor (FGF) expression is also under study. FGF signaling has been implicated in myeloma pathogenesis, but its role appears to vary depending on the stage of disease. Thalidomide impedes the activity of basic FGF, in turn inhibiting angiogenesis, but this effect may not be clinically significant. Additional study of the effects of FGF in multiple myeloma and the effects of thalidomide on FGF is needed.

Clinical studies in patients with multiple myeloma have confirmed the disease-modifying effects of thalidomide. Recently, the national MM6 Australian multicenter study compared the combination of thalidomide, zoledronic acid, and prednisone therapy after stem cell transplantation with control therapy of zoledronic acid and prednisone alone. After randomization, the number of patients in the thalidomide group who developed T-cell clones, and the number of T-cell clones present in these patients, was significantly higher than the number receiving control therapy. Detailed data from this study have not yet been published, but the large Intergroupe Francais du Myelome (IFM) trial[1] demonstrates prolonged progression-free survival with thalidomide maintenance therapy.

The information presented in this publication summarizes the effects of thalidomide alone and describes its synergistic effects with conventional therapies for multiple myeloma, including chemotherapy and dexamethasone. The combination of thalidomide, bortezomib, doxorubicin, and dexamethasone has been widely studied. In a pivotal trial, this combination was associated with a 20% remission rate in patients who were refractory to other treatments.[2] Various other combinations, such as thalidomide, vincristine, doxorubicin, and dexamethasone, as well as thalidomide, etoposide, and cyclophosphamide, are also reviewed. Studies of these combination regimens have revealed that the addition of thalidomide improves overall response rates and survival. Early treatment with thalidomide combination regimens has been shown to reduce paraprotein levels, indicating response to treatment, and increase remission rates. Current data suggest that patients who are already in remission before their transplant and remain in remission after the first transplant do not benefit from double transplantation. Studies to date indicate that thalidomide used in combination with chemotherapy and dexamethasone significantly improves outcomes, even in patients who are refractory to conventional cytotoxic therapeutic regimens.

References

1. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance therapy with thalidomide after autologous transplantation for myeloma: second analysis of a prospective randomized study of the Intergroupe Francophone du Myelome. Haematologica 2005; 90(Suppl 1):17. Abstract.
2. Zangari M, Barlogie B, Jacobson J, Shaugnessy J, Sawyer J, McCoy J, et al. VTD regimen comprising Velcade (V) + thalidomide (T) and added DEX (D) for non-responders to V+T effects a 57% PR rate among 56 patients with multiple myeloma (M) relapsing after autologous transplant. Blood 2003; 102:830. Abstract.