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Thalidomide and lenalidomide in multiple myeloma

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Multiple myeloma is a treatable but not necessarily a curable plasma-cell cancer. After decades of minimal progress, two new classes of drugs with novel mechanisms of action – immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib) – have been introduced for the treatment of this disease. Thalidomide and lenalidomide have shown great activity as single agents and in combination with glucocorticoids for the treatment of chemotherapy-refractory myeloma. Thalidomide – and more recently lenalidomide – in combination with dexamethasone have shown promising results as induction therapy. These drugs can easily be combined with other chemotherapeutic agents to potentiate the anti-myeloma effect. The immunomodulatory function of these drugs can be successfully exploited to control residual disease during remission. Thus, both thalidomide and lenalidomide have ushered in a new era of optimism in the management of this incurable cancer.

Key words: multiple myeloma; lenalidomide; thalidomide; immunomodulatory drugs (IMiDs); front-line therapy; relapsed or refractory myeloma; renal failure.

Multiple myeloma is a hematologic malignancy caused by clonal proliferation of plasma cells. For decades treatment has been palliative, as the conventional chemotherapeutic agents seldom induced complete remissions and disease invariably recurred and became refractory to therapy.[1] When dose-intensive therapy with melphalan and stem-cell rescue was applied to patients $\leq$70 years of age, 25–50% of them achieved a complete remission with attendant improvement in remission duration and life expectancy by a couple of years.[2] Just when progress with conventional chemotherapy

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seemed at a standstill, two new classes of drugs — namely, immunomodulators (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib) — have become available for the treatment of myeloma and are changing the landscape of the treatment of this disease.

THALIDOMIDE AND LENALIDOMIDE

Thalidomide was the first novel agent that was discovered to be active in the treatment of chemotherapy-refractory myeloma.[3] The precise mechanism of its antitumor activity is yet to be understood. However, thalidomide offered the first proof of principle that a drug which shows minimal direct cytotoxicity against tumor cells in vitro can have a profound antiproliferative effect by its action in the tumor microenvironment.[4,5] Thalidomide inhibits production of tumor necrosis factor α (TNF-α) by activated monocytes, down-regulates expression of cell adhesion molecules and inhibits angiogenesis. Thalidomide also has an immunomodulatory effect. By providing co-stimulation of T cells, it activates $CD8^+$ T cells with induction of interleukin 2 (IL-2) and interferon-γ (IFN-γ) production; it also has an immunosuppressive effect by down-regulation of pro-inflammatory cytokine production (IL-1, TNF-α, IL-6) by monocytes and induction of IL-10 production. It also stimulates natural killer (NK) cell activity against autologous myeloma cells.[6] The immunomodulatory drugs (IMiDs) are thalidomide analogues that were developed as potent anti-TNF-α agents that retained the immunomodulatory and anti-cancer effect while reducing the toxicity associated with thalidomide. Lenalidomide is a third-generation IMiD compound that has been approved for the treatment of MDS and very recently received approval for the treatment of multiple myeloma. Lenalidomide (CC5013) has been shown to be several orders of magnitude more potent than thalidomide in its direct apoptotic effect against myeloma cells, as well as in inhibition of inflammatory cytokine production and stimulation of T cells and NK cells.[7] It does not cause sedation, bradycardia, or constipation, and the incidence of neuropathy is lower. However, it is more myelosuppressive than thalidomide. Both drugs are associated with increased incidence of deep-vein thrombosis (DVT) and thromboembolism, especially when combined with dexamethasone and anthracycline.[8] Preclinical models indicate synergy between thalidomide and its analogs with glucocorticoids (dexamethasone, prednisone), bortezomib and alkylating agents.[5] This observation has been translated successfully in the clinic in the form of thalidomide and lenalidomide combination therapies with superior response and durability.

RELAPSED AND/OR REFRACTORY MM

Singhal and coworkers were the first to report on the observation that thalidomide was effective in relapsed and/or refractory myeloma.[3] In their phase-II clinical trial patients with refractory myeloma were treated with thalidomide in the dose range 200–800 mg/day. The response rate was 30% among the 169 patients enrolled on this study, including near complete remission (CR) or CR rate of 14%; the event-free survival (EFS) and overall survival (OS) at 2 years were 26% and 48% respectively. Moreover, 14% of the patients had their best ever response to thalidomide. Myelosuppression was minimal.[9] These observations have been subsequently confirmed by other investigators (Table 1). The responses were durable for a median of 8–12 months, and life expectancy was improved to 12–15 months. For these patients thalidomide is literally a life-saving drug.