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Lenalidomide (Revlimid®) in patients with cutaneous T-cell lymphoma

Thalidomide and its analogue lenalidomide

Lenalidomide [3-(4'aminoisoindolin-1'-one)-1-piperidine-2, 6-dione, Revlimid®] is the lead compound in a new class of agents which are known as the immunomodulatory drugs.[1] Lenali-domide has a similar chemical structure to thalidomide. Both drugs have a comparable *in vitro* profile; however, lenalidomide is more potent. The US Food and Drug Administration (FDA) has approved lenalidomide for the treatment of patients with transfusion dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with the deletion of 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.[2] In addition, it is FDA approved for the treatment of patients with multiple myeloma who have failed at least one prior therapy.[3] Due to its structural similarities to thalidomide, a known human teratogen, lenalidomide is approved for marketing only under a special restricted distribution program called RevAssist℠.

The anti-tumor effects of lenalidomide may be attributable to several potential mechanisms of action.[4] *In vitro*, lenalidomide inhibits the production by monocytes of pro-inflammatory mediators, including tumor necrosis factor (TNF-α), interleukin IL-1β, IL-6, and IL-12. It elevates production of IL-10 and inhibits expression of cyclooxygenase-2 (COX-2) and releases prostaglandin E_2 (PGE_2). In a spectrum of *in vitro* and *in vivo* studies, lenalidomide increased the proliferation and production of IL-2 and interferon-γ (IFN-γ) by T cells, and enhanced T cell and NK cell-mediated killing of tumor cells. The proliferation of hematopoietic tumor cell lines, including multiple myeloma, Burkitt's lymphoma, MDS, acute myeloid leukemia, and non-Hodgkin's lymphoma are inhibited by lenalidomide. *In vivo* tumor growth models have demonstrated that lenalidomide inhibits growth of multiple myeloma cells and the inhibition of angiogenesis by lenalidomide has resulted in reduced growth of solid tumors. In myeloma, lenalidomide has been demonstrated to inhibit vascular endothial growth factor and to reduce adhesion of myeloma cells to bone marrow stroma.

Lenalidomide is rapidly absorbed with the maximum concentration occurring between 0.6 and 1.5 hours post-dose. Co-administration with food delays absorption somewhat, but does not alter the extent of absorption. The mean half-life of elimination increases with increasing dose,

from approximately three hours at the 5 mg dose up to approximately nine hours at the 400 mg dose. Steady state levels are achieved by Day 4. Seventy percent of the orally administrated dose of lenalidomide is excreted by the kidneys. Cytopenias are the primary adverse events associated with the administration of lenalidomide, particularly in subjects with compromised bone marrow. However, these are manageable with dose interruptions and reductions. Other side effects include malaise, fatigue, diarrhea, rash, and muscle cramps. An increased risk of deep-vein thrombosis has been witnessed when lenalidomide is combined with steroids. A "flare" phenomenon has been observed in chronic lymphocytic leukemia prior to disease response.[5] The recommended starting dose for patients with MDS is 10 mg. Patients with multiple myeloma typically receive 25 mg daily for three weeks followed by a one week rest period.

We have conducted a trial in cutaneous T-cell lymphoma.[6] A total of twenty-five patients were enrolled between April 2005 and July 2008 and are evaluable for response and toxicity. The first fifteen patients received 25 mg lenalidomide daily for 21 days of a 28-day cycle. Beginning in October 2006 patients entering the trial had a standard lenalidomide dose of 10 mg with dose escalation of 5 mg with subsequent cycles based on response and toxicity (max. dose 25 mg). Response was assessed after every cycle using Composite Assessment (CA) of Index Lesion Disease Severity for skin lesions, absolute Sézary cell count for quantification of circulating malignant lymphocytes and/or CT scans for measurement of adenopathy or visceral disease. The median patient age was 60 years (range, 47-83), 14 females/11 males, and patients had received a median of 6 prior treatment regimens (range, 2-9). On study, clinical stages were IB (6), IIA (1), IIB (7), III (7), and IVA.[4] Seven patients have achieved a partial response

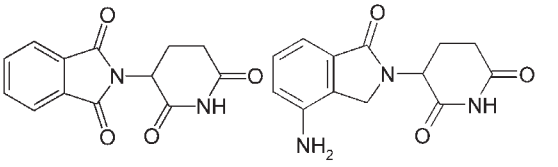

Figure 1.

(defined as a CA ratio less than or equal to 0.5 with no new clinically abnormal lymph nodes, no progression of existing clinically abnormal lymph nodes, and no new cutaneous tumors). Responding patients received a median of 9 cycles of therapy (range, 4-13 cycles); median time to best response was 6 months (range, 1-12 months), four patients discontinued therapy as a result of progressive disease and three patients as a result of toxicity. Eight patients had stable disease ≥ 4 months (median 5m; range 4-9 months). Twelve patients went off study as a result of progressive disease, seven as a result of toxicity, and six secondary to personal preference. A re-growth of disease-related hair loss was observed in some patients. The most common side effects were anemia, fatigue/malaise, skin burning, pruritus, diarrhea and lower leg edema. Results from our clinical trial indicate that lenalidomide shows clinical activity in patients with advanced CTCL with a toxicity profile similar to that previously reported. The mechanism of the observed anti-tumor effects remains unclear. An initial flare reaction manifested by a temporary increase in the size, number and discomfort of skin lesions and/or tender swelling of lymph nodes and/or increase in Sézary cell count was noted in some patients during the first cycle of treatment and/or each cycle for the remainder of therapy with subsequent improvement of symptoms and/or disease. Correlative biologic studies will include analysis of anti-angiogenic and immuno-modulatory activity on skin biopsies and peripheral blood samples.

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