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

C. QUERFELD
T.M. KUZEL
J.GUITART
S.T. ROSEN

Department of Medicine, Division of Hematology/ Oncology and Department of Dermatology, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

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] Lenalidomide 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 agents for 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] Currently, approval is being sought from the FDA 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™.

Lenalidomide's anti-tumor effects 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 vitro*. *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 5mg dose up to approximately nine hours at the 400mg 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* phenomena has been observed in chronic lymphocytic leukemia prior to disease response. The recommended starting dose for patients with MDS is 10 mg. Patients with myeloma typically receive 25 mg daily for three weeks followed by a one week rest period. We have initiated a trial in cutaneous T-cell lymphoma. To date, fifteen patients have been enrolled between April 2005 and June 2006 and are evaluable for response and toxicity. All patients received 25 mg lenalidomide daily for 21 days of a 28-day cycle. 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 61 years (range, 47-83) and patients had received a median of 6 prior treatment regimens (range, 2-9). Five patients have achieved a partial response (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). Six patients have experienced minor responses such as regression of cutaneous tumor lesions, improved lymphadenopathy, and skin improvement from initial generalized erythroderma to less severe erythema with less scaling. A re-growth of disease-related hair loss was observed in 4 patients. Four patients developed progressive disease with new and/or recurrence of indicator lesions. The most common side effects were anemia, fatigue/malaise, skin burning, pruritus, and lower leg edema. Four patients developed grade III fatigue/malaise requiring dose interruption. Two patients developed grade III neutropenia requiring treatment with G-CSF in one patient. One patient discontinued treatment after one cycle because of neurological symptoms (slurred speech) possibly related to the study drug. Preliminary data of our clinical trial indicate that lenalidomide shows clinical activity in patients with advanced CTCL with a manageable toxicity profile. However 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 almost all patients during the first cycle of treatment and/or each cycle for the

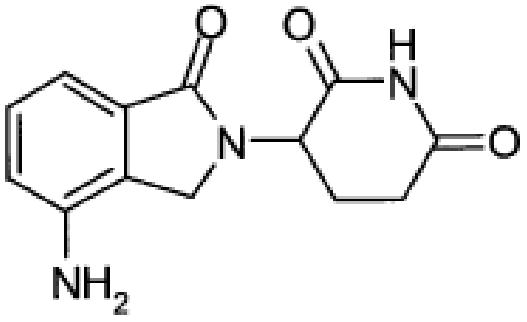

Figure.

remainder of therapy with subsequent improvement of symptoms and/or disease. The cause of this phenomenon has not been studied and could be related to the co-stimulatory or cytotoxic activity of lenalidomide and represent an immune response against the disease with enhanced $CD8^+$ T-cell and NK-cell cytotoxic activity, but may, in fact, represent a combination of cytotoxic and cytokine-mediated events. The potential immunomodulatory mechanisms underlying these observations will be investigated with correlative studies as the trial progresses. Accrual is ongoing.

References

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