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Lenalidomide as a Steroid Sparing Agent in a Myelodysplastic Syndrome Patient with Refractory Sweet Syndrome

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Abstract

Malignancy associated Sweet syndrome (acute febrile neutrophilic dermatosis) accounts for approximately 20% of all cases of Sweet syndrome and is characterized by painful, erythematous inflammatory papules and nodules that can precede, coincide or follow malignancies with predilection for hematologic malignancies (mainly acute myeloid leukemia and myelodysplastic syndrome). Corticosteroids are the cornerstone of treatment with exquisite response which has made many clinicians to include steroid responsiveness as one of the diagnostic criteria. However, recurrence can occur with tapering of steroids often needing a suppressive prophylaxis with unacceptably high dose of steroid for longer term. In addition, recurrence following tapering of steroids is a unique feature of malignancy associated Sweet syndrome occurring in two-third of patients. There is a paucity of effective steroid sparing strategy in the treatment of this disorder. Here we report a patient with myelodysplasia and refractory sweet syndrome successfully treated with low dose lenalidomide with resolution of skin lesions, improvement in hemoglobin level, allowing rapid and successful tapering of steroid and improvement in hyperglycemia. Immunomodulatory agents such as lenalidomide may have activity against sweet syndrome associated with myelodysplastic syndrome and therefore deserve further clinical investigation.

Case Presentation

A 63-year-old white man with past medical history of hypertension and atrial fibrillation developed painful cutaneous lesions on his upper arms and back and was initially diagnosed as "erythema nodosum". He was started on oral steroids and required greater than 40 mg prednisone a day to control the lesions. He developed diabetes mellitus after receiving prednisone for six months. Multiple attempts to taper the steroids below 20mg of prednisone per day were associated with rapid flare up of the painful skin lesions. He failed numerous agents including adequate trials of colchicine, methotrexate and various non-steroidal anti-inflammatory agents including indomethacin. The lesions were described as red painful papules and nodules involving upper and lower extremities and trunk. A repeat biopsy of the right forearm lesion showed evidence of edema and neutrophilic infiltration consistent with the diagnosis of Sweet syndrome. He was referred to rule out the possibility of an underlying hematologic neoplasia associated with Sweet syndrome. Hematology evaluation revealed hemoglobin 10.1gm/dL, hematocrit 30%, MCV 97 fL, white blood cell count 8,300/mm^3 with 55% neutrophils, and platelets count of 202, 000/mm^3. He has not had prior blood transfusion. Physical examination was remarkable for tender erythematous lesions measuring 2cm on the right thigh and left upper chest. No splenomegaly, hepatomegaly or lymphadenopathy noted. He was on 20mg daily of prednisone at this time with persistent painful skin lesions.

Peripheral blood smear revealed hypogranular neutrophils with abnormal nuclear segmentation including occasional pseudo Pelger-Huët anomaly, occasional giant hypogranular platelets, tear drop forms and basophilic stippling of red cells. A bone marrow aspirate and biopsy revealed a hypercellular marrow with morphologic evidence of trilineage dysplasia without an increase in blasts forms. Conventional karyotyping showed normal male karyotype and Fluorescent in-site hybridization (FISH) analysis failed to reveal any myelodysplastic syndrome (MDS) associated abnormalities. It was classified as MDS of International Prognostic Scoring System (IPSS) 0 based on presence of trilineage dysplasia without blasts and without chromosomal abnormality and presence of one lineage cytopenia (anemia).

The patient was started on lenalidomide 5mg three times a week in an attempt to taper prednisone. Over the course of next four months, the prednisone was tapered to 5 mg daily without any flair up of the cutaneous lesions. Moreover the hemoglobin increased to 13gm/dL, HbA1c decreased to 6.5% (from 10.6% pre-lenalidomide) and weight decreased by 20Lbs. Patient was instructed to further

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decrease prednisone to 2.5mg daily which was associated with flair up of Sweet lesions in upper extremities, neck, trunk and lower extremities. Prednisone was increased to 5 mg daily and lenalidomide maintained at 5mg three times a week without further exacerbation of Sweet syndrome. He has been on this combination for over three years and has tolerated it well. He reports excellent diabetic control and good quality of life. He continues to have normal complete blood counts with morphologic evidence of trilineage dysplasia.

Discussion

Lenalidomide (Revlimid; Celgene Corporation, Summit, NJ, USA) is an immunomodulatory (IMiD) agent indicated for treatment of multiple myeloma (MM), AL amyloidosis, MDS with 5q- and relapsed/refractory mantle cell lymphoma. It is also in active clinical investigation for the treatment of chronic lymphoid leukemia (CLL), non-Hodgkin's lymphomas (NHL), Hodgkin's lymphoma and some solid tumors. Lenalidomide has been found to be associated with various dermatologic adverse reactions ranging from mild self-limiting rash to very rare life-threatening reactions including angioedema [1], Stevens-Johnson syndrome (SJS) [2,3] and a single case of toxic epidermal necrolysis (TEN) [2]. There have been three reported cases of lenalidomide associated sweet syndrome in three separate hematologic malignancies (one patient each with MM [4], CLL [5] and agnogenic myeloid metaplasia) [6]. We report on the use of lenalidomide to treat a patient with MDS associated Sweet syndrome. Thalidomide has been previously described to cause complete resolution of cutaneous lesions of Sweet syndrome that were resistant to high dose steroids, metronidazole, dapsone and methotrexate in a patient with MDS [7] indicating possible class activity of IMiD against sweet syndrome associated with MDS.

Corticosteroids have remained the agents of choice for the treatment of recurrent Sweet syndrome since its initial description by Robert D Sweet in 1964 [8]. There remains an unmet need for an effective alternative for patients who are intolerant to steroids or require maintenance therapy to prevent recurrence in patients with Sweet syndrome. The IMiD may be an effective class of drugs that can potentially be used to spare steroid in sweet syndrome due to MDS.

Alternative agents have been proposed either as an upfront therapy when steroid is contraindicated or as a maintenance strategy when steroid sparing is desired. These agents include colchicine, dapsone, potassium iodide and indomethacin. In a retrospective analysis of 20 patients with non-malignancy associated Sweet syndrome, colchicine in a daily dose of 1 to 1.5mg given for a mean duration of 2 weeks was associated with durable effectiveness in 18 patients without relapse in 2 to 10 years (median 8.5 years) of follow up [9]. However, the efficacy of colchicine in malignancy associated Sweet syndrome is unknown. Toxicity including diarrhea and myelosupression may limit its use as steroid sparing agent in hematologic malignancies such as MDS or AML where cytopenia is a common finding either as a feature of disease or as a result of therapy. Dapsone [10], potassium iodide [11] and indomethacin [12] have also been used to treat Sweet syndrome but their experience in malignancy-associated sweet syndrome is limited. Lenalidomide has been approved for transfusion-dependent anemia in the setting of low or intermediate-1 risk MDS associated with a deletion 5q cytogenetic abnormality. Use of lenalidomide in this setting is associated with complete cytogenetic response in 45% of patients and transfusion independence in 67% of patients [13]. A phase 2 study of lenalidomide in transfusion-dependent, low or intermediate-1 risk MDS patients with karyotypes other than deletion 5q (non-5q- MDS) also showed cytologic and cytogenetic responses albeit at a much lower rate than that was seen in 5q- MDS patients including transfusion independence in 26% of MDS patients with normal karyotype [14]. These studies attest that the malignant MDS clone is susceptible to lenalidomide therapy. Recent *in vitro* study has shown that IMiD lenalidomide and pomalidomide down-regulate PU.1, a key transcription factor involved in granulocyte differentiation causing transient maturation arrest of myeloid precursors explaining the neutropenia observed in MM patients receiving lenalidomide [15]. In addition, thalidomide and lenalidomide are known to have anti-inflammatory, anti-angiogenic and immunomodulatory effects. The response of Sweet lesions in MDS patient of Browning et al. [7] receiving thalidomide and our patient receiving lenalidomide may have been due to the direct anti-inflammatory and or immunomodulatory effect on the cutaneous lesions in addition to the known disease modifying effect of these agents by acting on the malignant MDS clone in bone marrow. In our case, the low dose lenalidomide was well tolerated allowing a rapid tapering of prednisone to 5mg daily. Recently, lenalidomide in combination with chemotherapy was reported to show improvement of cutaneous Sweet lesions in a chemotherapy refractory overlap syndrome (MDS/MPN) patient evolving from prior essential thrombocythemia (ET) [16].

Conclusion

Preclinical correlative studies are needed to underscore the probable mechanisms before testing IMiD such as low dose lenalidomide in clinical studies in patients with Sweet syndrome in the setting of MDS. The prior case reports of lenalidomide associated Sweet syndrome may reflect the heterogeneity of the underlying mechanisms associated with the development of Sweet syndrome and may represent associations rather than causation [4-6,17]. There remains a dearth of steroid sparing strategy in hematologic malignancy associated sweet syndrome [17]. Our case suggests that there may be a role for the use of lenalidomide in the treatment of Sweet syndrome in patients with MDS and possibly other myeloid malignancies.

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