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REVIEW

Cutaneous adverse reactions to lenalidomide

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Abstract Lenalidomide is an immunomodulatory drug (IMiD) used principally in the treatment of multiple myeloma (MM), myelodysplastic syndromes (MS) and amyloidosis.

Adverse reactions related to lenalidomide include myelosuppression (mainly neutropenia but also thrombocytopenia), gastrointestinal problems, skin eruption, atrial fibrillation and asthenia, decreased peripheral blood stem cell yield during stem cell collection, venous thromboembolism, and secondary malignances. In this review we focused our attention on the cutaneous adverse reactions to lenalidomide.

Introduction

Lenalidomide is an immunomodulatory drug (IMiD) used principally in the treatment of multiple myeloma (MM), myelodysplastic syndromes (MS) and amyloidosis. Furthermore, several studies on the association between lenalidomide and the standard therapies are ongoing in patients affected by diffuse large B-cell lymphoma.[1] However, lenalidomide is the most potent analogue of thalidomide but causes fewer adverse reactions, thus showing a better safety profile.

These drugs have direct antitumour action and indirect immunomodulatory and anti-angiogenic effects. In

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fact, through induction of cell cycle arrest and caspase-dependent apoptosis they may kill myeloma multiple cells. Moreover some authors have shown that they also target a stem cell-like subpopulation.[2]

More specifically, IMiDs directly induce apoptosis of MM cells via caspase-8 activation, block MM cell–bone marrow stromal cell interactions, inhibit secretion of cytokines in the bone marrow responsible for MM cell growth and survival, and inhibit angiogenesis.[3–5]

Moreover, IMiDs increase NK cell cytotoxicity against MM cells, induce T-cell proliferation, modulate IL-12 production and interfere with the action of several cytokines, such as IL-2, IFN-γ, IL-1β, IL-6, GM-CSF, and TNF-α.[6–8]

Adverse reactions related to lenalidomide include myelosuppression (mainly neutropenia but also thrombocytopenia), gastrointestinal problems, skin eruption, atrial fibrillation, asthenia, and decreased peripheral blood stem cell yield during stem cell collection when lenalidomide is used after a long period of time.[9]

In addition, when lenalidomide is combined with dexamethasone or other conventional cytotoxic agents, there is an increase in the incidence of venous thromboembolic events.[2] The venous thromboembolic risk with lenalidomide–dexamethasone is further increased with concomitant erythropoietin.[10]

Finally, there is an increased incidence of secondary malignancies in newly diagnosed MM patients receiving lenalidomide plus melphalan/prednisone.[11,12]

Literature review

Known complications of cutaneous areas are due to lenalidomide side effects.

A retrospective study found incidences of skin eruptions, generally mild, in 43% of 23 patients with MM treated with lenalidomide and dexamethasone and in 29% of seven with MM on lenalidomide alone.

The skin eruptions were of morbilliform, urticarial, dermatitic, acneiform, and undefined forms. Severe skin eruptions required permanent discontinuation of lenalidomide therapy in two patients. In 23 patients (72%), skin eruptions occurred in the first month after therapy was initiated while delayed-onset skin eruptions occurred in nine (28%).[13]

Celgene Corporation has received 12 reports of Stevens–Johnson Syndrome (SJS), three reports of Erythema multiforme (EM) and one report of toxic epidermal necrolysis (TEN) among approximately 57,000 patients who received lenalidomide from its launch on the market on December 27, 2005 through to June 26, 2008. Ten SJS cases were spontaneous reports from US health care professionals while the other two cases where reported by the US investigator-initiated trials. The 12 cases occurred in seven women and five men with a median age of 63.5 years (range, 50–83 years).

Erythema multiforme occurred in three patients (two women and one man, aged 85, 74, and 70 years, respectively) after 7, 24 and 112 days from the start of the treatment with lenalidomide in association with dexamethasone. Cutaneous lesions were accompanied by blistering, sores, mucosal involvement, crusting, and fever. Two patients were hospitalised, and one died.

Toxic epidermal necrolysis was reported in an 85-year-old woman hospitalised 18 days after initiating lenalidomide with dexamethasone for multiple myeloma.[14]

Stevens–Johnson Syndrome was described in a patient with multiple myeloma who received lenalidomide in combination with prednisolone. In literature, there are various reports as to the correlation between SJS and lenalidomide treatment.[13–20] Among these cases, one was particularly interesting because the patient experienced a complete remission of the multiple myeloma after the severe cutaneous reaction. A 69-year-old woman with multiple myeloma presented erythema, mucocutaneous tenderness and haemorrhagic lesions which developed into a SJS at the end of the first cycle of lenalidomide and prednisolone combination treatment regimen. Subsequently, lenalidomide treatment was stopped and replaced with dexamethasone and clodronate. Upon patient follow-up, serum and urine were negative for M protein as was immunofixation and <5% plasma cells in bone marrow were found; thus complete remission was achieved.

It may be that the cytokine storm caused by SJS could have determined the induction of idiotype-specific T cells able to act against the myeloma cells.[17]

Another case of SJS was described in a 51-year-old man affected by primary plasma cell leukaemia and treated with lenalidomide and dexamethasone.[18] Boruah instead described the onset of a severe cutaneous manifestation probably induced by lenalidomide in a 73-year-old Caucasian female undergoing induction therapy for multiple myeloma. In this case lenalidomide was substituted with bortezomib for her induction therapy and the patient did not experience any further cutaneous reactions.[19]

In most cases the therapy with lenalidomide is not completely discontinued but only temporarily interrupted or reduced in dosage.

An interesting study was conducted to evaluate the histocompatibility antigen genes, HLA-A, B, C, DRB1 and DQB1, of Italian MM patients with dermatologic adverse reactions after lenalidomide treatment.

Seven women and three men (mean age 68 ± 10.81 years) were included in two different controlled trials. They were randomised to receive lenalidomide-prednisolone or lenalidomide-dexamethasone with a specific treatment scheme.

Three patients experienced dermatologic complications: urticaria, EM and SJS. The polymerase chain reaction (PCR) amplification followed by sequence specific primers (SSP) HLA typing was performed and the analysis of the Italian patients showed that the two severe dermatologic complications were both related to HLA-DRB*1501 and HLA-DQB1*0602, whereas the patient with urticaria presented HLA-DRB1*1502 and HLA DQB1*0601.The authors concluded that application of HLA-genotyping as a screening tool before prescribing lenalidomide could contribute in evaluating the risk factors and preventing severe lenalidomide-induced dermatologic reactions.[20]

A particularly rare manifestation was described in a 60-year-old patient who received lenalidomide for the treatment of a plasmacytoma. After four months of treatment, red papules appeared on the extremities and the trunk