Long-term complete remission in a multiple myeloma patient after Stevens-Johnson syndrome due to lenalidomide therapy

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To the Editor,

Myeloma tumor cells may contain a multitude of tumor antigens that can stimulate an increased repertoire of anti-tumor T cells and lead to an induction of stronger antimyeloma responses.

Myeloma plasma cells may in fact express MHC class-I antigens; adhesion molecules, such as CD44, CD56, CD54, and VLA-4; signaling or costimulatory molecules CD40 and CD28; as well as the Fas antigen (CD95). Some of the plasma cells also express HLA-DR, CD80, and CD86 [1,2].

Results from recent research have indicated that myeloma cells are susceptible to T cell-mediated cytolysis. In the post-allograft relapse setting, in which myeloma patients are chemotherapy refractory, long-lasting disease remission has been achieved after infusion of donor lymphocytes, a phenomenon termed graft-versus-myeloma (GVM) effect [3]. This GVM effect is closely associated with graft-versus-host disease (GVHD), and donor-derived alloreactive and tumor-specific T cells are believed to mediate these effects.

Here, we describe a patient with multiple myeloma (MM) who experienced a long lasting complete remission after Stevens-Johnson syndrome (SJS) onset while receiving lenalidomide in combination with prednisolone. We discuss the possible mechanisms that led to the long-lasting remission.

Case report

A 69-year-old woman was admitted to our department in July 2010 because of back pain caused by the compression fracture of the lumbar spines. Serologic tests and bone marrow studies confirmed the pathologic diagnosis of MM, immunoglobulin G (IgG K) type, stage III. The serum IgG level was high (7701 mg/dL) and the serum level of β2 microglobulin was 8.537 mg/L. A skeletal survey was positive for lytic areas in the skull, clavicles, scapulae, ribs and spine, with collapse of the third lumbar vertebra. Immunohistochemical stains revealed that 80% of the marrow's cellularity comprised CD138 positive plasma cells, which exhibited monotypic K light chain restriction. Moreover, myeloma cells were positive for CD40, CD45, CD56, CD31, and CD117. Fluorescent in situ hybridization revealed the presence of t(4:14) translocation.

The patient was included in a controlled trial, and she was randomized to receive a lenalidomide-based combination regimen, consisting of lenalidomide 10 mg daily on days 1 to 21, followed by seven days off. Prednisolone was cycled at 25 mg on alternate days. Treatment cycles were repeated every 28 days. Thromboprophylaxis was given using enoxaparin 40 mg/day.

After the end of the first cycle, she presented erythema, mucocutaneous tenderness and hemorrhagic erosions. Two days later, an epidermal detachment appeared, presenting as blisters and areas of denuded skin on the legs (about 5% of the total body surface area). Involvement of the buccal mucosa occurred too.

Histological analysis confirmed SJS diagnosis. Subsequently, lenalidomide treatment was stopped. Steroid medication therapy was continued with 80 mg methylprednisolone, and antiseptics were administered topically. All dermal and mucosal lesions healed without scarring after 30 days [4,5].

Following the resolution of the dermatological complication, the patient was treated with dexamethasone 40 mg orally four days per month and clodronate 100 mg a week intramuscularly. Serum M-protein was no longer detectable from September 2010, and the patient achieved complete hematological remission. The serum IgG level was 874 mg/dL, and the serum level of β2 microglobulin was 3100 mg/L. Bone marrow analysis showed a

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plasma cell infiltration equal to 6%. Two years after SJS, in August 2012, the patient remained in complete response, with no M protein in serum and urine, negative immunofixation and $< 5\%$ plasma cells in bone marrow.

An immunophenotypic study performed periodically by flow cytometry showed the presence of a constant increase of CD8 +, DR + and CD56 + cells.

Discussion

Idiotype proteins are tumor-specific antigens, and active immunization against idiotypic determinants on malignant B cells has produced resistance to tumor growth in transplantable murine B-cell lymphoma and plasmacytoma [6,7]. The presence of idiotype-specific T cells in the peripheral blood of patients with MM or with the benign form of the disease, monoclonal gammopathy of undetermined significance (MGUS), has been studied by several reports [8,9], and idiotype-specific T cells at a low frequency were detected in 90% of patients with MM or MGUS [10].

T cells, especially $CD8^+$ lymphocytes, have been identified to play an important role in the onset of SJS, a process that is most likely mediated by cytokines [11]. Recently, functionally active $CD94/NKG2C^+$ cells were detected in the blister fluid but also in the peripheral blood of patients with SJS. This activating receptor might be involved in triggering cytotoxic T cells in the acute stage of the disease [12].

An interpretation that allows us to explain the long remission of our patient is not easy, however, it is possible that the cytokine storm that accompanies the SJS can lead to the induction of idiotype-specific T cells able to act against the myeloma cells.

Various clinical immunotherapy treatments have been tested in MM. Most of these have focused on targeting idiotype-specific immunity. Idiotype-based vaccines have been shown to induce or enhance idiotype-specific immunity, indicating that the vaccines are able to elicit a specific immune response. However, clinical response is still a rare event, occurring only in a minority of treated patients, suggesting that the elicited or enhanced immunity is still too weak to cause significant tumor destruction [13]. Recently, anyway, other antigens which might create an additional therapeutic target have been identified. Several studies have in fact shown that the cancer-testis antigens MAGE-3 and NY-ESO-1 may be expressed by myeloma cells [14], while, other antigens, such as MUC-1, sperm protein 1, and HM1.24, may also be expressed on myeloma cells, and MHC-restricted antigen (MUC-1 and Sp17)-specific CTLs have been generated from myeloma patients that were able to lyse myeloma cells [15–17].

A better understanding of the mechanisms that regulate the cytotoxic response against myeloma cells could lead to a better therapeutic approach of the disease.

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