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Daratumumab Before and After Haploidentical Hematopoietic Stem Cell Transplantation in Relapsed/Refractory Multiple Myeloma: Is the Right Strategy to Overcome Microenvironment Impact in Multiple Myeloma?

Francesca Fazio, Luisa Quattrocchi, Luciano Fiori, Gianfranco Lapietra and Maria Teresa Petrucci*

[*]Department of Translational and Precision Medicine, Division of Hematology, Sapienza University of Rome, Rome

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ABSTRACT

Novel drugs, approved during the last decade for the treatment of relapsed/refractory multiple myeloma (RRMM), including proteasome inhibitors and immunomodulatory drugs, have changed the scenery and today represent the standard of care. Importantly, MM currently remains a chronic hematologic disease and all patients with MM unfortunately experience relapse or, very often, become progressively refractory to all available drugs. In order to overcome the natural relapse or treatment resistance, ongoing challenges to identify novel therapeutic strategies and new compounds with different mechanisms of actions are necessary. In the last years, scientific attention has been drawn increasingly to immunotherapeutic strategies with the potential for improved targeting for MM clonal plasma cells to maintain a prolonged response and to achieve a possible cure for MM patients. Allogenic stem-cell transplantation can be considered the first immunotherapy offering the potential for prolonged survival time in MM patients. Immunotherapy is currently the key strategy for the treatment of hematologic malignancies, especially multiple myeloma. Daratumumab is the first in class human IgG1K monoclonal antibody targeting CD38 with specific tumor activity associated with immunomodulatory mechanism and is approved as a single agent and in combination with standards of care for the treatment of RRMM. Instead, little is known about the use of daratumumab as a bridge therapy to allo-HSCT and further studies evaluating the efficacy and the safety of daratumumab-based therapy before and after allo-HSCT are warrented.

Keywords: Multiple myeloma, Relapsed/Refractory, Allogenic stem cell transplantation, Monoclonal antibody

CASE PRESENTATION

Here in, we report a case of a young patient with relapsed/refractory multiple myeloma (RRMM) treated with daratumumab in combination with lenalidomide and dexamethasone (DRd) before and after allogenic stem cell transplantation (allo-HSCT).

In October 2015, a 45-year old man was referred to our Hematology Department with a history of persistent bone pain over several months. Computed tomography showed multiple osteolytic bone lesions located at the level of the pelvis, the lumbo-sacral tract and the ribs.

Initial lab work showed no anemia (Hb 13 g/dL), a mild increase in creatinine (1.3 mg/dL) and calcium levels (10.8 mg/dL). The remaining blood tests were otherwise normal. A fully MM work up was pursued. Serum free light chain (FLC) analysis showed kappa (k) light chain of 2010 mg/dL, lambda (λ) light chain of 5.6 mg/dL and FLC k/λ was 358.9 with an immunoglobulin (IgA) k monoclonal band detected in urine and serum immunofixation (serum monoclonal protein was 1.7 g/dL) and an increase in beta 2 microglobulin levels (5.2 mg/dL). A bone marrow biopsy revealed the presence of 80% of restricted CD138+ plasma cell for the k light chain. According to the 2016 International Myeloma Working Group (IMWG) the patient met criteria for MM and was diagnosed with ISS stage II IgA-K MM.

Induction therapy regimen based on bortezomib (1.3 mg/m^2

Corresponding author: Maria Teresa Petrucci, Division of Hematology, Azienda Policlinico Umberto I, Via Benevento 6, Rome, Italy, Tel: 0649974430; E-mail: petrucci@bce.uniroma1.it

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on days 1, 4, 8 and 11), thalidomide (200 mg/die) and dexamethasone (40 mg on days 1-4 and 8-11) every three weeks was immediately started. Based on the IMWG response criteria, the patient had a partial response after completing six cycles of therapy. The main toxicities during the treatment course were fever and pneumoniae, after the second cycle. The patient was then hospitalized and started specific antibiotic therapy with Piperacilline/Tazobactam.

At the end of the induction therapy, peripheral blood stem cells were collected following cyclophosphamide ($2g/m^2$) associated to granulocyte colony stimulating factor mobilization (9.3×10^6 /kg). In May 2016, and January 2017, high dose melphalan conditioning at 200 mg/m^2 was administered in two separate doses, and was followed by peripheral blood autologous stem cells transplantation (ASCT) after 2 days. Based on the IMWG response criteria, the patient confirmed a partial response after completing a tandem ASCT.

In September 2018, after nearly 2 years since ASCT, the patient developed a swelling at the level of the skull. A fully MM work up was repeated, and an increased level of monoclonal protein in serum and urine was detected. Bone marrow biopsy revealed the presence of 20% of restricted CD138+ plasma cell for the k light chain. However, according to the IMWG criteria, the patient experienced MM relapse. Considering timing (<24 months), age, and localization of the relapse, we considered treating the patient with monoclonal antibody anti-CD38+ (Daratumumab). According to the data of POLLUX trial [1], the patient began treatment with daratumumab (16 mg/Kg) associated with lenalidomide (25 mg/die) and dexamethasone (40mg/weekly). Meanwhile, according to the consensus recommendations of the IMWG and the European Society for Blood and Marrow Transplantation, human leucocyte antigens typing was performed on the patient and his siblings. Two haploidentical siblings were identified. In July 2019, after 11 cycles of DRd regimen therapy, based on IMWG criteria, a partial response was confirmed. In September 2019, the patient received a common myeloablative conditioning regimen based on thiotepa (day -7 and -6; 10 mg/kg) – busulfan (day -5, -4; 3.2 mg/kg) – fludarabine (day -5, -4 and -3; 50 mg/m^2/die) and then he underwent allo-HSCT from one of the haploidentical donors (graft source was bone marrow). Graft-versus-Host-Disease (GVHD) prophylaxis consisted of post-transplantation cyclophosphamide 50 mg/kg at day +3 and +5, while mycophenolate mofetil was used from day 0, and cyclosporine from day -1. Neutrophil and platelet engraftment was achieved at day +15 and day +20, respectively. In April 2020, the patient, in partial remission after haploidentical HSCT (haplo-HSCT), started consolidation therapy with DRd regimen therapy. To date, the patient is alive and no acute, or chronic, GVHD has been reported.

DISCUSSION

Novel drugs, approved during the last decade for the treatment of RRMM, including proteasome inhibitors and immunomodulatory drugs, have changed the scenery and today represent the standard of care [2]. However, as MM progresses, a reduction in the duration, and the depth of response is observed after each treatment relapse [3]. It is known that patients eventually relapse and some subgroups of patients, such as those with high-risk cytogenetic abnormalities, may not achieve the same benefits as standard-risk patients. According to these considerations, therapy must be tailored and based on patient and disease factors [4].

Several studies have demonstrated that MM is associated with immune dysfunction, including immune evasion through the expression of immune checkpoint ligands on clonal plasma cells, elevated adenosine receptor and activity, immune suppression through myeloid-derived suppressor cells (MDSCs), and regulatory T cell activity (Treg). MDSCs and regulatory B cells (Bregs) are present in the MM microenvironment and contribute to tumor growth, immune evasion, neo-angiogenesis and production of suppressive cytokines [5].

It is known that CD38 is highly and uniformly expressed on MM surface cells and, at low levels, on normal myeloid and lymphoid surface cells, as well as on platelets and red blood cells. CD38 is also present on other immune cells, such as MDSCs and Bregs. In addition, a novel subgroup of T cells was identified to express high levels of CD38 and demonstrated higher autologous T-cell suppressor activity than other T-cells. Indeed, the subpopulation of CD38-positive Tregs is more potent in suppressing T cell proliferation when compared to CD38-negative Tregs [6]. All the CD38-positive immunosuppressive cell populations are associated with decreased immune function and MM progression.

CD38 is a transmembrane glycoprotein with ectoenzymatic activity, and functions as an adhesion molecule and a receptor. Based on the high CD38 expression on MM cells, it is identified as potential therapy target and this has triggered the development of several CD38 antibodies [4].

Daratumumab is the first in class human IgG_1K monoclonal antibody targeting CD38 with specific tumor activity associated with immunomodulatory mechanism, [7] and is approved as a single agent and in combination with standards of care for the treatment of RRMM [1,8]. Daratumumab have classic Fc-dependent immune effector mechanism, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis [9]. All these mechanisms of action are dependent on CD38 expression on MM pathological cells. Administration of daratumumab has proved to reduce CD38-positive immune suppressor cells, including Tregs, NK cells, regulatory B cells and MDSCs. Although, the CD38 decrease

occurs rapidly in all patients, after the first daratumumab infusion, the incidence of complete response and minimal-residual disease negativity increases over time. This data also suggests that the activity of daratumumab is not totally dependent of the presence of CD38 on MM clonal plasma cells, and expresses its immunomodulatory effects through the significant reduction of CD38-positive Bregs, Tregs and MDSCs. In daratumumab-treated patients, Tregs are reduced, while helper and cytotoxic T cells are increased. It is expected that the increase in T cell frequency and activity, leads to a better host-anti-tumor immune response [5,6]. This data confirms that daratumumab-mediated elimination of CD38+ immune cells may reduce local immune suppression within MM bone marrow microenvironment, and allow positive immune effector cells to expand and enhance the antitumor response.

Despite improvements in the MM outcome, and in the depth and response duration following subsequent lines of therapy, MM remains an incurable disease and none of these therapies are able to eradicate the plasma cell clone. It is reasonable to consider allo-HSCT as a treatment strategy for young patients with high-risk disease and an available donor [10]. Allo-HSCT is potentially effective by virtue of a graft-versus-myeloma (GvM) effect, and haplo-HSCT with post-transplantation cyclophosphamide as GVHD prophylaxis could be considered an option, but currently, there is little data available regarding this treatment [11]. However, the role of allo-HCT in MM is controversial with studies showing conflicting results [12]. Both allo-HCT and donor leukocyte infusion are associated with acute and chronic GVHD after transplantation [13]. However, an immunomodulatory effect derived from chronic GVHD may contribute to improve disease control through GvM and prolonged overall survival [14]. Novel anti-myeloma agents are of therapeutic interest to facilitate GvM effect and improve survival due to their immune-modulating properties. Daratumumab binds CD38 immune cells, included T cells that could be implicated in GVHD. In daratumumab-treated patients, Tregs are reduced while helper and cytotoxic T cells are increased, and a decrease in Tregs has been associated with the onset of GVHD after allo-HSCT. Nevertheless, the use of daratumumab-based therapy after allo-HSCT is not well described, and its potential role on GVHD development is unknown. Nikolaenko et al performed a multicenter retrospective study to evaluate 34 patients with MM who received daratumumab for treatment of MM relapse after allo-HSCT. Daratumumab-based therapy poses an important concern for GVHD flare in consideration of its specific effects on T cell regulation. The incidence of GVHD after daratumumab is low and this data supports the use of daratumumab as therapy after allo-HSCT [15]. Instead, nothing is known about the use of daratumumab as a bridge therapy to allo-HSCT and, to our knowledge, this is the first report of a RRMM patient treated with anti-CD38 monoclonal antibody before, and after, allo-HSCT. Further studies evaluating the efficacy and the safety of daratumumab-based therapy (as a single agent, or in combination), before and after allo-HSCT are warranted.

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