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Case Report
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A Young Patient with Mantle Cell Lymphoma has been Cured by Myeloablative Hematopoietic Stem Cell Transplantation

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Abstract

The diagnosis of Mantle Cell Lymphoma (MCL) is rarely made in young adults as the disease is most commonly encountered in middle age and elderly individuals. The currently available therapeutic modalities including autologous Hematopoietic Stem Cell Transplantation (HSCT) are not curative. Allogeneic HSCT with Reduced-Intensity Conditioning (RIC) therapy is usually offered to transplant-eligible patients taking into consideration their old age and comorbid medical conditions. We report a young patient who failed to achieve Complete Remission (CR) of her MCL after receiving 8 cycles of intensive cytotoxic chemotherapy, commenced in August 2008, at King Fahad Specialist Hospital (KFSH) in Dammam, Saudi Arabia. Later on the patient had an allogeneic HSCT with myeloablative conditioning therapy performed at King Faisal Specialist Hospital and Research Center (KFSH-RC) in Riyadh in February 2009. During her follow-up at KFSH in Dammam, she developed hepatic Graft Versus Host Disease (GVHD) that was successfully treated with steroids and cyclosporine-A. Eighteen months after her allograft, the patient had complete resolution of her residual disease. Her MCL is still in CR more than 6 years after her HSCT.

Keywords: Mantle cell lymphoma; Cytotoxic chemotherapy; Hematopoietic stem cell transplantation; Myeloablative conditioning; Graft versus host disease

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Introduction

MCL is a rare but distinct subtype of B-cell Non-Hodgkin's Lymphoma (NHL) [1-4]. It accounts for 2-10% of all NHLs [1,3-7]. It has male predominance with male: female ratio of 2-4:1 [1-4]. It mainly affects middle age and elderly individuals with the median age between 60 and 70 years [1-3,8]. MCL usually presents with stage III or IV disease. Bone Marrow (BM) involvement, extensive lymphadenopathy and splenomegaly are the usual presenting manifestations [4]. However, MCL may present with pancytopenia, leukocytosis, and extra-nodal sites such as gastrointestinal involvement [4].

MCL is characterized by the chromosomal translocation t(11,14)(q13;q32) which results in the over expression of the cell cycle regulator cyclin-D1 that, in turn, causes a disorder of regulation in cell proliferation [1-4,7,8]. Although most patients with MCL follow an aggressive clinical course, a subset of patients may have a more indolent disease course [8]. Despite the recently introduced aggressive therapeutic interventions, the overall prognosis is usually poor and the median overall survival is usually 3 to 7 years [4,6,9].

Case Presentation

A 23 year old Saudi female was diagnosed to have MCL; stage IV B bulky disease; at KFSH in Dammam in early 2006. She presented with constitutional symptoms and generalized lymphadenopathy. The initial diagnosis was made on the basis of a lymph node biopsy. Unfortunately, the patient discharged herself against medical advice and she preferred to have herbal and traditional therapies instead. However, on 26th of August 2008, she was readmitted to KFSH in Dammam with progression of her lymphoma in the form of extensive lymphadenopathy, particularly in the cervical area, hepatosplenomegaly and BM involvement causing pancytopenia: White Blood Cell (WBC) count of 3.4 x 10^9/liter (L), Hemoglobin (Hb) of 4.9 grams/L and platelet (PLT) count of 44 x 10^9/L). Lymph node and BM biopsies showed heavy infiltration by intermediate-sized lymphocytes that were positive for: CD20, cyclin-D1, CD5, CD10, BCL2, BCL6 and CD3.

The proliferation index, Ki67, was 30%. Other investigations showed: LDH of 355 units/L, normal immunoglobulin levels, normal serum protein electrophoresis and no evidence of central nervous system involvement. After re-establishing the diagnosis of MCL, the patient received 8 cycles of hyper-CVAD regimen of chemotherapy [cyclophosphamide, vincristine, doxorubicin, dexamethasone] alternating with high-dose methotrexate and cytarabine following which a remarkable reduction in the bulk of her disease was achieved, but she was left with approximately 15% residual disease. Later on, the patient was referred to KFSH&RC in Riyadh for HSCT. As the patient was young without comorbid medical conditions and because she had residual disease at the end of her chemotherapy and as she was found to have a healthy and an HLA identical sibling donor, it was decided to go ahead with an allogeneic HSCT rather than an autologous HSCT. She received a myeloablative allogeneic HSCT in February 2009. The conditioning therapy was composed of 12 Gy Total Body Irradiation (TBI) and cyclophosphamide. After recovery of her blood counts, she moved back to the Eastern Province to have follow-up at KFSH in Dammam. Four months following her successful allograft, she developed localized herpes zoster infection, which was treated successfully with intravenous then oral acyclovir for 2 weeks. Six months post-transplant, the patient developed moderate GVHD of the liver, manifested by 3 to 4 fold elevation in her serum gamma-glutamyl transpeptidase and alkaline phosphatase levels. This form of GVHD was treated successfully for 3 months with cyclosporine-A and oral prednisolone. A chimeric study was done 6 months post-HSCT and it showed a 100% donor chimerism for lymphoid as well as myeloid cells. One year post-HSCT, the patient also underwent restaging evaluation with Computerized Axial Tomography (CAT) scan which showed further regression in the extent of her residual disease to about 5%. Six months later, a new CAT scan was performed and it showed no evidence of disease below or above the diaphragm. Then the patient continued to have regular follow-up at our outpatient clinic and she remained clinically stable. She was last seen at the HSCT out patient clinic at KFSH in Dammam on the 9th of June, 2016. She was totally asymptomatic and her physical examination showed no new abnormality. Her complete blood count showed: WBC: 5.87 x 10^9/L, Hb: 13.4 grams/L and PLT: 249 x 10^9/L. Her renal, hepatic and bone profiles were all within normal limits. No new medication was prescribed and a new follow-up appointment was scheduled.

Discussion

There is no standard induction or first-line treatment for MCL [10]. The first-line therapy in MCL is usually adapted to age and comorbid medical conditions [11]. The available chemotherapeutic as well as targeted therapies for MCL include: R-hyper-CVAD; R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone); R-DHAP (rituximab, dexamethasone, high-dose cytarabine and cisplatinum), R-MACLO-IVAM-T (rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, cytarabine, ifosfamide, cytarabine and etoposide followed by thalidomide maintenance); lenalidomide; bortezomib; bendamustine; flavoperidol; temsirolimus; abexinostat; ibrutinib and the combination of cladrabine plus rituximab or mitoxantrone [2,12,13]. R-hyper-CVAD has been shown to be tolerable and effective induction therapy for untreated patients with MCL [10].

In patients with MCL, high-dose chemotherapy and autologous HSCT have been performed both upfront and at relapse with varying degrees of success [14]. In patients subjected to autologous HSCT, CR can be achieved in approximately 80% of cases, but almost all patients including responders will ultimately relapse [11,13]. Poly-chemotherapy plus rituximab followed by autologous HSCT has become the standard of care in young patients with MCL as this strategy, compared to chemotherapy alone, has demonstrated higher response rates in addition to improved progression-free survival as well as the possibility of improved overall survival [11-13,15-18].

Advanced-stage MCL is a disease for which no proven curative therapeutic strategy currently exists [14,18]. However, patients with advanced-stage MCL treated with high-dose chemotherapy plus rituximab followed by autologous HSCT have been shown to have more prolonged survival compared to patients treated with conventional chemotherapy [18]. Unfortunately, relapse/refractory MCL carries a dismal prognosis [5]. For patients with relapsed/refractory MCL, the results of autologous HSCT remain unsatisfactory, while the timely application of non-myeloablative allogeneic HSCT may be curative [4,9]. In patients with relapsed/refractory MCL having chemo-sensitive disease, allogeneic HSCT may be curative given the graft versus-MCL provided by this form of transplantation [11].

The first evidence of graft versus malignancy in MCL was demonstrated in the late 1990s and this proved the efficacy of allogeneic HSCT in patients with MCL [19,20]. Later on, several studies have shown that in patients with MCL, allogeneic HSCT is the only therapeutic strategy with curative potential [1,5,11,15,21,22]. However, the main drawbacks of myeloablative allogeneic HSCT are: (1) the procedure is only feasible for a small number of patients, (2) the associated toxicities in the form of GVHD and infectious complications and (3) the relatively high treatment-related mortality (TRM). Hence, RIC-allogeneic HSCT is adopted in an attempt to reduce the toxicities and the high TRM associated with myeloablative allografts [15,20,21,23].

Studies have shown that myeloablative allogeneic HSCT is a feasible and a promising therapeutic option for younger patients with MCL who are fit for the procedure and who have no comorbid medical conditions, while RIC-allogeneic HSCT is a valid choice for patients who are still fit for the procedure but are old and have medical comorbidities [5,11,20,21,24]. The indications for RIC-allogeneic HSCT in MCL include: (1) relapsed but chemo-sensitive disease including multiple relapses, (2) refractory disease or disease poorly responsive to high-dose chemotherapy and (3) MCL relapsing after autologous HSCT [5,9,11,23,25]. The conditioning therapies utilized in RIC-allogeneic HSCT include low-dose TBI, fludarabine and alemtuzumab [5,21]. The outcome of allogeneic HSCT in patients with MCL can be improved further by: (1) optimal patient selection, that is, younger patients with less comorbidities and who are more fit for the procedure, (2) optimal timing of HSCT, (3) the use of less toxic conditioning therapies, and (4) close monitoring of chimerism and optimal use of donor lymphocyte infusions [13,23-25].

Our patient had advanced disease at presentation which failed to respond completely to eight cycles of intensive cytotoxic chemotherapy. The decision to proceed with a myeloablative allogeneic HSCT rather than an autologous HSCT was based on the following: (1) the young age of the patient, (2) the absence of comorbid medical conditions, (3) the availability of an HLA-identical sibling for allograft, and (4) having a significant residual disease which was likely to cause an early post-HSCT relapse of her disease. The development of GVHD was effective not only in controlling

her residual disease but also in preventing later relapse due to the associated GV lymphoma effect.

In conclusion: in young patients with MCL having no comorbid medical illnesses and having an HLA-identical donor, allogeneic HSCT with myeloablative conditioning therapy should be considered as a potentially curative therapeutic intervention. In patients with MCL subjected to allografts, graft versus disease effect may counteract disease relapse and may abolish residual disease.

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