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A Young Patient with Refractory Multiple Myeloma and Dialysis-Dependent Renal Failure has been Cured by Non-Cryopreserved Autologous Stem Cell Transplantation Followed by Live-Related Kidney Transplantation

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Abstract

Management of patients with multiple myeloma having dialysis-dependent renal failure, particularly if the disease is refractory to several lines of therapy, is a difficult task. Cure of such patients represents a real challenge to the treating team. In late November 2009, the diagnosis of multiple myeloma was made in a young patient who had been receiving regular hemodialysis for end-stage renal disease. His myeloma was refractory to four lines of therapy and it responded partially to the fifth line of treatment. Thereafter, the patient received a non-cryopreserved autologous hematopoietic stem cell transplantation which brought his myeloma under more optimal control. One year later, he received live-related kidney transplantation. During his subsequent follow-up for fifty four months post-renal transplantation at King Fahad Specialist Hospital in Dammam, Saudi Arabia, no complication has been encountered. As the case is complicated, the literature review will be detailed in order to discuss the various aspects related to care of the patient presented the patient presented. To our knowledge, this is the first report of cure of refractory multiple myeloma and chronic renal failure by non-cryopreserved autologous stem cell transplantation followed by live-related kidney transplantation.

Keywords: Multiple myeloma; Chronic renal failure; Hematopoietic stem cell transplantation; Engraftment syndrome; Maintenance therapy; Kidney transplantation; Immunosuppressive therapy

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Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy [1,2]. It accounts for 1% of all cancers and 10% of malignant hematological disorders [3,4]. MM is a disease that affects plasma cells and can lead to various clinical manifestations and occasionally life-threatening complications [1,3]. The diagnostic criteria of MM include: (1) clonal bone marrow (BM) plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma, and (2) at least one of the following: evidence of end-organ damage such as hypercalcemia, anemia, lytic bone lesions and renal insufficiency; clonal BM plasma cells $\geq 60\%$; involved: uninvolved serum free light chain ratio ≥ 100 and >

one focal lesion on magnetic resonance imaging [2,3]. High-risk features at the diagnosis of MM include: (1) cytogenetic abnormalities that include: 17p deletion, t(14,16) and t(14,20), (2) international scoring system stage II or III, (3) presence of comorbid medical conditions that limit therapy, and (4) renal failure, high

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serum lactic dehydrogenase and plasma cell leukemia [3,5]. In patients with MM having high-risk features, the incorporation of bortezomib into the multi-agent chemotherapeutic regimen VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide) has proven to be effective not only in induction therapy prior to hematopoietic stem cell transplantation (HSCT), but also in consolidation and maintenance therapy post-autologous HSCT (auto-HSCT) [6,7]. This combination therapy may induce near complete remission and increase the 2 year survival rates to more than 80% [6]. The use of bortezomib, thalidomide and lenalidomide has dramatically changed the outcomes of patients with relapsed and refractory MM [8]. Treatment options for patients with relapsed and refractory MM have benefited from the development of new targeted agents and they include: (1) HSCT as patients with stable refractory disease subjected to HSCT have been shown to have an outcome comparable to those with chemosensitive disease, (2) using new therapeutic regimens that the patient has not been exposed to previously, (3) re-challenge with previously used chemotherapeutic regimens; (4) experimental therapy offered as part of a clinical trial, and (5) the use of new novel therapies such as the immunomodulatory agents, proteasome inhibitors and monoclonal antibodies either as single agents or in drug combinations [8-10]. Currently, three drug regimens are recommended as frontline therapy for patients with MM as they have proven to be effective and safe [4,5,11]. Examples of the triplet drug regimens are: VRD (bortezomib, lenalidomide and dexamethasone), VCD (bortezomib, cyclophosphamide and dexamethasone) and VTD [4]. However, the most promising triplet drug regimen is VRD [4,5,11].

In adult patients with MM, high-dose chemotherapy followed by auto-HSCT has been associated with longer progression-free survival than VRD therapy alone [11]. The use of a combination therapy that incorporates newer proteasome inhibitors, next-generation immunomodulatory agents and potent monoclonal antibodies along with HSCT tailored according to minimal residual disease could improve the outcomes of adults with MM [11]. In patients with high-risk features, carfilzomib, lenalidomide and dexamethasone (KRD) is an alternative to VRD regimen [3]. The recently approved novel therapeutic agents for use in the treatment of MM include: (1) newer proteasome inhibitors such as carfilzomib and ixazomib, (2) histone acetylase inhibitors such as panobinostat and vorinostat, (3) new immunomodulatory drugs such as pomalidomide, (4) monoclonal antibodies such as daratumomab and elutuzumab, (5) Bruton tyrosine kinase inhibitors such as ibrutinib, (6) alkylating agents such as bendamustine, (7) interleukin-6 inhibitors such as rituximab and (8) phosphoinositide 3-kinase inhibitors [1,2,9]. Substantial evidence indicates that bortezomib, high-dose dexamethasone ± a third drug such as cyclophosphamide, thalidomide or doxorubicin is an appropriate option to be used in induction therapy for patients with MM having any degree of renal impairment [12].

Case Presentation

A 37 year old Saudi male was diagnosed to have end-stage renal

disease (ESRD) at AlQateef hospital and he was commenced on regular hemodialysis in July 2009. In November 2009, the patient was referred to King Fahd Specialist Hospital (KFSH) in Dammam for renal transplantation. He was diagnosed to have MM, IgA kappa, stage III. His diagnostic investigations showed: Hb: 82 gram /liter (g/L), IgA: 55.4 g/L, B₂M: 5.1, ESR: 135, 70% monoclonal plasma cells on BM biopsy, hyperdiploidy of chromosomes 7 and 15, hypercalcemia and serum protein of 117 g/L without evidence of bone disease. The lines of therapy given were as follows: (1) Induction therapy in early December 2009 with bortezomib and dexamethasone. A total of 8 cycles were administered without achieving any response. (2) The first salvage therapy was given in early September 2010 and it was composed of lenalidomide, cyclophosphamide and dexamethasone. A total of 3 cycles were given, but without positive responses. (3) The second salvage, VAD (vincristine, doxorubicin and dexamethasone) chemotherapy, was administered in late November 2010. A total of 4 cycles were administered and the patient achieved partial response of his disease as his IgA: 24.3 g/L and a new BM biopsy showed 23% plasma cells. (4) The third salvage therapy, bendamustine 100 mg/m²/day IV for 2 days each month in addition to weekly dexamethasone, was commenced in April 2011. After receiving a total of 4 cycles, progression of disease was encountered as serum IgA was 23 g/L and a new BM biopsy showed 70% plasma cells. (5) The first cycle of the fourth salvage, VTD-PACE protocol of therapy with 25-50% dose reduction, was commenced in August 2011. After receiving 3 cycles of VTD-PACE, very good partial response (VGPR) was achieved as serum IgA became 3.9 g/L and BM plasma cells decreased to 15%.

After discussions in the HSCT meeting and with the renal transplantation team, it was concluded that the available therapeutic options in presence of an human leucocyte antigen (HLA) and blood group identical sibling donor, his sister, were: (1) an auto-HSCT for partially controlled MM followed by maintenance or a tandem auto-HSCT within 6-12 months, or (2) an allogeneic HSCT and a renal allograft from the same donor that could be performed either simultaneously or sequentially, or (3) maintenance therapy in the form of bortezomib, lenalidomide or thalidomide. A decision was made after discussion with the patient and his family to go for an autologous HSCT in order to control his myeloma first then to decide on the next step at a later stage, so the patient underwent stem cell mobilization with granulocyte-colony stimulating factor (G-CSF) after 4th cycle of VTD-PACE.

Two sessions of apheresis were performed to harvest his autologous HSCs. The total stem cell dose collected was 2.39×10^6 kilogram (kg). The patient received a single dose of IV melphalan: 140 mg/m² as conditioning therapy on the 5th of December 2011. On 6/12/2011, the patient received his non-cryopreserved stem cells. He engrafted his neutrophils, with G-CSF, on day 13 and his platelets on day 15 post-HSCT respectively. The following complications were encountered in the early post-HSCT period: mucositis and severe engraftment syndrome in the form of capillary leak syndrome that was treated successfully with corticosteroids. Till day 100 post-HSCT, no new complications were encountered, his biochemical profile apart

from renal function normalized and a new BM biopsy showed that plasma cells decreased to < 5%. Throughout his follow-up at our institution, the patient continued to have regular hemodialysis and adjustments of doses of medications were made as needed.

Subsequent plans included a live-related renal allograft and a second autologous stem cell collection, but despite the use of plerixafor, the new stem cell collection failed. The patient received a live-related renal allograft on 23/12/2012. A peripheral blood stem cell collection from the kidney donor, his sister, was performed 3 months after the renal transplantation and the apheresis product was cryopreserved for future use in case of disease relapse. During subsequent follow up, no problems were encountered for 54 months post-renal allograft. In order to keep the myeloma of this patient under control and to avoid adverse outcome on the transplanted kidney, the patient has been receiving maintenance therapy with bortezomib. Additionally, the patient was kept on tacrolimus, mycophenolate mofetil and low-dose prednisolone as immunosuppressive therapy for his renal allograft. He was last seen at the HSCT clinic on 29/05/2017. He was asymptomatic and his physical examination did not reveal any new abnormality. His blood counts, renal function, hepatic and bone profiles were all within normal limits. He was continued on the same triple immunosuppressive therapy as well as bortezomib maintenance therapy and a new follow-up appointment was scheduled.

Discussion

Auto-HSCT performed early in the disease course or at first relapse is considered the standard of care treatment for younger patients with newly diagnosed MM due to improvement in event-free survival and overall survival (OS) when compared to conventional chemotherapy alone [4,13,14]. Eligibility for auto-HSCT is determined by age, performance status and presence as well as severity of certain comorbid medical conditions [13]. The implementation of auto-HSCT in conjunction with novel therapies has revolutionized the management of MM and has markedly altered the natural history of the disease by improving response rates, duration of responses and OS [14,15].

Peripheral blood HSCs collected by apheresis are the preferred source of stem cells to guarantee rapid engraftment [13,14]. The goal of apheresis is to collect approximately $6-8 \times 10^6$ CD 34+ cells/kg body weight of the recipient which is considered sufficient for two or tandem transplants [13,14]. The minimum acceptable HSC dose for successful transplantation is $2-3 \times 10^6$ CD34+ cells/kg [14,16-19]. The recommended conditioning regimen for MM is high-dose melphalan 200 mg/m² for patients with normal renal function, but for patients with serum creatinine >2.0 mg/dL at the time of transplantation, the dose of melphalan should be reduced to 140 mg/m² [13]. Maintenance therapy is recommended following auto-HSCT with lenalidomide being the preferred therapy for standard-risk patients while for intermediate-and high-risk patients, bortezomib is the maintenance therapeutic agent of choice [13].

For most types of transplants, cryopreservation of HSCs is necessary and is an essential component of the clinical protocol

[20]. Dimethyl sulfoxide (DMSO) is widely used as a cryopreservative agent for various types of stem cells and other body tissues [21]. DMSO has the following adverse effects: skin irritation; garlic breath or body odor; abdominal pain, nausea, vomiting and diarrhea; bronchospasm, chest tightness and dyspnea; altered heart rate and blood pressure, arrhythmias, heart block and myocardial ischemia; various degrees of neurotoxicity, renal and hepatic dysfunction and death [20,21]. Also, it has in vitro toxicity in the form of induction of red blood cell hemolysis and reduction in platelet aggregation and activity [21].

Auto-HSCT without cryopreservation of stem cells has the following advantages: (1) simplicity of implementation and allowing auto-HSCT to be performed entirely as outpatient, (2) reduction of transplantation costs, (3) reducing the time between the last induction therapy and high-dose chemotherapy, (4) prevention of DMSO toxicity, (5) expansion of the number of medical institutions performing stem cell therapies, and (6) no significant reduction in the viability of collected HSCs provided stem cell infusion is made within 5 days of apheresis [14,22]. On the other hand, non-cryopreserved auto-HSCT has the following disadvantages: (1) limitation of the use of standard high dose schedules such as BEAM (BCNU, etoposide, cytarabine and melphalan) employed in auto-HSCT for lymphoma, (2) plenty of coordination between various teams is needed regarding timing of stem cell mobilization, apheresis, administration of conditioning therapy and stem cell infusion, and (3) inability to store part of the collection and reserving it for a second auto-HSCT in case a rich product is obtained [14,22].

The high relapse rates reported after auto-HSCT have been attributed to the assumption that graft versus tumor (GVT) effect is lacking in the auto-HSCT setting [23]. Recent studies argue in favor of the existence of an autologous GVT effect without the detrimental complications of graft versus host disease (GVHD) [23]. Although graft versus myeloma (GVM) effect has been well documented in the allogeneic HSCT setting, recent studies have provided evidence of its existence even in the setting of auto-HSCT [23-27]. MM represents a genuine malignancy with disrupted immune surveillance. Hence, the immunotherapeutic interventions are potentially valuable in inducing GVM effect following HSCT [24].

Engraftment syndrome (ES) is a febrile illness that occurs within 4 days of neutrophil recovery following HSCT [28]. It was first described by Lee et al in a retrospective analysis of 248 patients with cancer undergoing auto-HSCT [29,30]. ES has also been described after allogeneic HSCT, but it has been more frequently reported following auto-HSCT [28,31,32]. The risk factors of ES include: MM and lymphoma as the underlying illnesses, previously administered chemotherapy and radiotherapy, faster engraftment and infusion of higher number of stem cells [14,28]. The clinical manifestations of ES resemble those of acute GVHD and they include: fever, skin rash, hepatic and renal dysfunction, transient encephalopathy, capillary leak syndrome and death [28,29,31,33]. ES has to be differentiated from autologous GVHD, infections as well as drug toxicity and radiation induced tissue damage [31]. ES is typically self-limited and it usually responds to corticosteroids, supportive care and other immunosuppressive

agents although intensive care and mechanical ventilation may be required in severe forms [29,31-33].

Renal impairment is a common complication of MM [34-37]. Between 30% and 50% of patients with newly diagnosed MM present with renal dysfunction while renal failure occurs in approximately 20%-30% of patients with MM at diagnosis and in more than 50% of patients with advanced disease. Also, up to 13% of patients with MM and renal failure require hemodialysis [34,38-40]. Additionally, renal impairment develops in 50% of patients with MM during the course of the disease [34]. In patients with MM, renal dysfunction can be attributed to: toxic effects of monoclonal light chains on the kidney, dehydration, hypercalcemia, hyperuricemia, nephrotoxic drugs, contrast media, hyperviscosity, cast nephropathy, myeloma cell infiltration, amyloid deposition and infectious complications [34,36,38,40,41]. In patients with MM renal dysfunction has been associated with shorter survival and early death [39]. In such patients, renal failure requiring hemodialysis in particular carries poor outcome and hence the degree of renal impairment significantly affects the prognosis [38,39].

Bortezomib, lenalidomide, thalidomide and corticosteroids are particularly effective in patients with MM having renal dysfunction or failure [34,36,41]. Even in MM patients having dialysis-dependent renal failure, bortezomib-based regimens can be safely used and can potentially reverse renal function and contribute to the improvement in outcome [35,39,42,43]. Bortezomib and high-dose dexamethasone regimen is considered the regimen of choice in patients with MM presenting with severe renal dysfunction or failure [34,38]. Doses of bortezomib and dexamethasone in patients with MM and renal failure are as follows: bortezomib 1.3 mg/m² on days 1,4,8 and 11 and dexamethasone 20 mg on days 1,2,4,5,8,9,11 and 12. Cycles can be repeated every 3 weeks [34,39].

Allogeneic HSCT is still the only curative therapeutic modality for MM, but has rarely been used in patients with renal failure [38]. High-dose melphalan (140 mg/m²) followed by auto-HSCT can be offered to patients with MM younger than 60 years with renal failure, but having chemosensitive disease and good performance status [34,37,40,44]. Even in MM patients having dialysis-dependent renal failure, high-dose chemotherapy followed by auto-HSCT has been successfully used and has been associated with late recovery of renal function and improved survival [38,45]. In patients with MM, renal function is one of the most important prognostic factors as renal failure has been associated with poor prognosis [46,47]. The degree and duration of renal failure significantly affect the chances of recovery of renal function [48]. Nevertheless, renal failure has no impact on the quality of stem cell collection and does not affect engraftment. Also, renal failure has no impact on the response of patients to chemotherapy [48].

Patients with renal failure are generally excluded from HSCT due to the possible occurrence of life-threatening complications that may be translated into unacceptable high transplant-related morbidity and mortality [46,49,50]. In patients with MM having dialysis-dependent renal failure, high-dose chemotherapy

and auto-HSCT have traditionally been contraindicated due to the following reasons: lower survival rates, higher short-term mortality, greater susceptibility to infectious complications, longer durations of hospitalizations and greatly compromised quality of life (QOL) [47]. MM patients having renal dysfunction and even those with dialysis-dependent renal failure should not be excluded from auto-HSCT as studies have proven not only the safety but also the effectiveness of high-dose chemotherapy followed by auto-HSCT in such group of patients [46,49,51,52]. Historically, the first auto-HSCT performed for a patient with MM and renal insufficiency was reported in the year 1997 [53].

Studies have shown that conditioning therapy with melphalan 140 mg/m² has an acceptable toxicity and is equally effective as melphalan dose of 200 mg/m² and that even high-dose melphalan (200 mg/m²) prior to auto-HSCT can safely be administered in patients with MM having ESRD as it has not been associated with toxicity or non-relapse mortality [45,51,54]. Hence, melphalan dose reduction may not be required [45,54]. In recent years, high-dose chemotherapy followed by auto-HSCT has been increasingly utilized in the treatment of patients with MM [49]. Auto-HSCT can also be offered to patients with MM having renal failure with an acceptable toxicity and with a significant improvement in renal function in approximately one-third of auto-HSCT recipients [45].

Kidney transplantation is the treatment of choice for most patients with ESRD as it is associated with improved survival and QOL compared to hemodialysis [55]. Even in patients with MM having renal failure, kidney transplantation is a therapeutic option in well-selected patients who achieve control of their disease and maintain a durable remission preferably for 3-5 years and have stable light chain levels but this option should be considered early in the course of the disease [36,37,41,56]. In patients with ESRD, kidney transplantation using induction therapies and standard triple drug immunosuppression has become an acceptable therapeutic modality to control acute graft rejection [57]. The formation of donor-specific antibodies (DSAs) and the evolution of antibody mediated rejection (AMR) may critically contribute to late graft loss [58]. Highly sensitized patients with reactive antibodies are difficult to transplant, hence they need desensitization as they are at increased risk of AMR [55]. Strategies to remove or decrease preformed antibodies include: intravenous (IV) immunoglobulins, plasmapheresis, IV corticosteroids, rituximab and rabbit anti-thymocyte globulin [55]. Recently, there is accumulating evidence in the form of numerous case series and anecdotal reports suggesting the efficacy of bortezomib in reducing the levels of DSA, improving renal function and preventing graft loss in patients with acute AMR [58]. Despite the limited experience with bortezomib in renal transplantation, it seems that the drug has a promising role not only in desensitization protocols, but also in rejection protocols as it induces depletion of plasma cells that produce anti-HLA antibodies [55].

Combined HSCT, predominantly auto-HSCT, and solid organ transplantation (SOT), predominantly renal transplantation, have been performed for patients having various hematological disorders such as plasma cell dyscrasias, BM failure syndromes

and leukemias as well as organ failure due to ESRD, liver failure or heart failure due to cardiomyopathies or other diseases [59-62]. Combined HSCT and SOT can be performed either simultaneously [59-66] or sequentially with either HSCT first followed by SOT [59,67-73] or SOT first followed by HSCT [59,60,74,75]. Thus, patients with MM having ESRD, either on regular hemodialysis or not, can be offered not only HSCT but also combined HSCT and renal transplantation either simultaneously or sequentially [59,63,64,67,68].

Recently, cellular therapies in the form of stem cells such as autologous BM-derived mesenchymal stem cells (MSCs) have become an attractive option to: (1) minimize immunosuppressive therapies, and (2) improve graft survival in recipients of SOT thus preventing morbidity and mortality associated with the use of immunosuppression [57,76,77]. These cellular therapies have been combined with steroids and everolimus [57,76,77]. In patients having acute kidney injury or chronic kidney disease due to various causes including autoimmune disorders, certain cellular therapies such as embryonic stem cells and MSCs have been successfully used to induce injury repair and other regenerative processes. These cellular therapies can be used alone or in combination with renal transplantation [78-81]. Additionally, not only auto-HSCT but also allogeneic HSCT have been performed in the treatment of autoimmune disorders having ESRD [79].

MSCs that can be obtained from BM, peripheral blood, umbilical cord blood and many other sources are capable of self-renewal and multi-lineage differentiation [78]. Multiple preclinical studies have demonstrated that MSCs could prevent renal injury and could promote renal recovery through immunomodulation as well as release of paracrine factors and microvesicles [78]. Also, studies in animal models of acute and chronic renal failure

have demonstrated the potential of MSCs to migrate into areas of inflammation, ischemia and tissue injury and due to their differentiation, regenerative and immunomodulatory properties they can ultimately improve renal function by promoting tubular proliferation and regeneration of damaged renal tissues [81-85].

The patient presented had MM which was refractory to four lines of treatment. His disease responded only partially to the VTD-PACE regimen. Receiving an auto-HSCT further improved the control of his disease. Having a non-cryopreserved autograft and the capillary leak syndrome which possibly gave him more GVM effect prevented the relapse of his MM. Keeping him on bortezomib maintenance not only helped in preventing myeloma relapse, but also maintained his renal allograft and prevented rejection of the transplanted kidney. So, in patients with MM, even those having dialysis-dependent ESRD, but who are young and have excellent performance status, aiming at cure of both diseases is a valid therapeutic option.

Conclusion

Young patients with MM, even those with refractory disease and those receiving hemodialysis for ESRD, deserve particular attention and should not be excluded from curative therapeutic interventions including combinations of novel therapeutics as well as combined HSCT and renal transplantation performed either simultaneously or sequentially.

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