Short Report

Autologous stem cell transplantation can potentially reverse dialysis dependence in patients with myeloma: Report of two cases and practical considerations

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ABSTRACT

Background. Autologous stem cell transplantation (ASCT) is potentially beneficial for patients with myeloma-related renal impairment but is associated with high rates of complications in dialysis-dependent patients and requires specific precautions.

Methods. Patients diagnosed with myeloma and concomitant dialysis-dependent renal dysfunction were admitted for ASCT after achieving at least partial response with bortezomib-based induction therapy. For both patients, mobilization consisted of granulocyte colony stimulating factor for 5 days and CD34 directed Plerixafor on Day 1. Melphalan was administered at a dose of 140 mg/m^2 and a pre-emptive session of haemodialysis was planned 24 hours after melphalan. Peripheral blood stem cell infusion was done after 24 hours. A central venous sample for blood gas analysis was obtained daily and ad hoc dialysis was planned at the earliest sign of metabolic acidosis (pH <7.35, HCO_3 <15 or K >6 mEq/L).

Results. Two patients with biopsy proven cast nephropathy and dialysis dependence (twice a week) were taken for ASCT with the above protocol. No variation from usual stem cell yield or engraftment kinetics was noted. Patient 1 (M, 49 years) achieved very good partial response post-transplant and has been dialysis free for 18 months post-ASCT. Patient 2 (M, 48 years) achieved negative immunofixation post-ASCT and was dialysis free for 9 months post-transplant, following which he requires one session of dialysis every 3–4 weeks for onset of uraemic symptoms.

Conclusions. ASCT in dialysis-dependent patients is associated with a higher risk of drug toxicity, infections and transplant-related mortality. Use of reduced dose melphalan, pre-emptive dialysis after 24 hours and monitoring for acidosis and symptoms of uraemia to identify acidosis at an early stage allows safe administration of high dose chemotherapy. A major proportion of patients can potentially achieve reduction or freedom from dialysis support post-transplant.

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INTRODUCTION

Renal impairment (RI) is observed in about 20%–25% patients with multiple myeloma at diagnosis, of which approximately 2% to 5% require haemodialysis.[1] Despite the efficacy of novel agents, several patients continue to have persistent RI and dialysis-dependence, which is associated with higher rates of complications and treatment-related mortality.[2] Till recently, dialysis-dependent (DD) RI was considered a contraindication to autologous stem cell transplantation (ASCT) and has gradually gained mainstream acceptance with demonstration of safety and efficacy in observational studies.[3] There is little Indian data available on the same. We report 2 patients with dialysis dependent RI who achieved dialysis independence post-ASCT with high dose melphalan.

METHODS

Transplant protocol

Patients diagnosed with myeloma and DD RI were admitted for ASCT after achieving partial remission (PR) or better with induction therapy. Stem cell mobilization was done with granulocyte colony stimulating factor (G-CSF) administered at a dose of 10 µg/kg/day for 5 days along with a single dose of Plerixafor on day 1 depending on peripheral blood CD34 counts. Melphalan was administered at a dose of 140 mg/m^2 and a session of pre-emptive haemodialysis was planned 24 hours later. Pre-melphalan hydration consisted of 2 L of intravenous normal saline. Peripheral blood stem cells were stored at 2 to 4 ^oC and infused after an interval of 24 hours. To determine indications for ad hoc dialysis, a central venous blood gas (VBG) sample was obtained daily, and dialysis was planned at any sign of metabolic acidosis (pH <7.35, HCO_3 <15) or hyperkalaemia (K >6 mEq/L). Dialysis was also done if a patient had any symptoms suggestive of uraemia. Antifungal and antiviral prophylaxis was given as per usual protocols. Empiric choice of antibiotics for febrile neutropenia included Cefoperazone–Sulbactam and Levofloxacin, to which Teicoplanin was added for fever persisting after 12–24 hours. Meropenem and Colistin were added for persistent fever after 48 hours or haemodynamic instability. Antibiotics were modified or de-escalated if results of blood cultures were available during hospital admission. For Colistin and Teicoplanin, a full loading dose was administered, followed by renal adjusted dosing. Transfusion thresholds were in keeping with current guidelines, and cut-offs of 7 g/dl for red blood cell transfusion and <10 000 cmm (<20 000 cmm if febrile or bleeding) for platelet concentrate

transfusion were followed. Irradiated blood products were mandated.[4]

RESULTS

Patient 1

A 49-year-old man was diagnosed with IgG Kappa myeloma with biopsy proven cast nephropathy at diagnosis. He was classified as R-ISS (Revised International Staging System) stage III due to b2m >5.5 mg/L and del17p on fluorescence in-situ hybridization (FISH). He was given Lenalidomide–Bortezomib–Dexamethasone (RVD) as initial therapy and required twice a week maintenance dialysis through a subclavian vein Perma-Cath. After 4 cycles of RVD, disease assessment was consistent with very good partial response (VGPR) and he was referred to us for ASCT. Pre-transplant, his creatinine range was 5–6 mg/dl, with an eGFR of 18 ml/minute on DTPA (Diethylenetriamine pentaacetate) scan. He underwent ASCT with the above protocol with a peripheral blood stem cell (PBSC) dose of 2.8 million/kg. He required three sessions of dialysis from Day +4 onwards based on the criteria listed above. He developed fever and hypotension on Day +7 for which he was shifted to the ICU for 72 hours for monitoring and inotropic support. Neutrophil engraftment was achieved on Day +10 and he was discharged uneventfully. After Day +100 of ASCT, he was given maintenance therapy with Bortezomib at a dose of 2 mg s.c. every 2 weeks. One year post-transplant, his creatinine ranges was 4–5 mg/dl without oliguria or uraemic symptoms and he has not required dialysis.

Patient 2

A 48-year-old man was diagnosed with lambda light chain myeloma with biopsy proven cast nephropathy and was on twice a week maintenance dialysis through a brachial fistula. R-ISS staging was not available as initial evaluation was performed elsewhere and baseline FISH was not available. Pre-transplant disease status was VGPR after 4 cycles of Bortezomib–Cyclophosphamide–Dexamethasone (VCD), with an eGFR of 33 ml/minute on DTPA scan. After admission, he received PBSC at a dose of 4 million/kg, and required two sessions of dialysis after he was noted to have acidosis on VBG on Day +5 and Day +9. He had grade III mucositis and achieved neutrophil engraftment on Day +14. He was also started on Bortezomib maintenance on Day +100 post-transplant. Post-transplant, his creatinine was 5–6 mg/dl, and he did not require haemodialysis for 6 months. After 6 months, he had gradual onset of uraemic symptoms, which required one session of haemodialysis every 3–4 weeks.

DISCUSSION

ASCT with high dose melphalan improves survival for patients with myeloma and is gradually gaining mainstream acceptance for patients with RI. Use of this procedure for patients with advanced chronic kidney disease (CKD) and those on haemodialysis can be further augmented with appropriate precautions.

A majority of patients undergo reversal of RI with timely initiation of novel agents, but RI can persist in patients where cast nephropathy has already set in.[5] It is essential to look for other causes of CKD, including diabetes mellitus and hypertension, both of which were absent in the above patients. Patient 1 was already on RVD at presentation, which was continued due to lack of any major adverse effects. Although Lenalidomide can potentially cause greater toxicity in RI, it can be safely administered with careful monitoring providing good efficacy.[6]

Based on published data, no major modification to standard PBSC mobilization is recommended. However, Plerixafor is excreted by the kidney and a lower dose of 0.16 mg/kg (usual dose 0.24 mg/kg) is associated with equivalent safety and efficacy in advanced RI.[7] Although melphalan is cleared through the kidneys, no clinically significant change in biological half-life has been observed in patients with CKD. The half-life of melphalan for patients with a creatinine clearance of <40 ml/minute and >40 ml/minute was found to be 1.9 and 1.1 hours, respectively, allowing safe reinfusion of stem cells after a 12–24 hour period.[8] Although this pharmacokinetic study utilized a dose of 100 mg/m^2 on consecutive days, it has been shown that a dose exceeding 140 mg/m^2 is associated with increased toxicity without conferring any added efficacy in patients with RI.[9] This is also reflected in a recent European Society of Bone Marrow Transplantation analysis, with most dialysis dependent patients receiving 140 mg/m^2 with equivalent clinical benefit.[10]

Pre-melphalan hydration represents another challenge, especially in oliguric patients and requires careful monitoring.[11] Use of a planned session of haemodialysis 24 hours after melphalan has been previously reported and can be done to prevent volume overload.[12] Patients with pre-existing RI are at a higher risk of acute kidney injury following melphalan administration (HR 7.01, 95% CI 2.0–24.0).[13] This requires maintenance of adequate hydration and diuresis post-melphalan and planning ad hoc haemodialysis at any signs of worsening renal function. We used a central VBG analysis to objectively detect early metabolic or lactic acidosis. VBG avoids recurrent arterial puncture and shows excellent concordance with an arterial sample for identification of acid–base disturbances, making it a pragmatic early warning system.[14]

Based on published series, about 20% to 30% patients achieve dialysis independence post-transplant.[3,15] The largest series spanning 20 years (1997 to 2017) noted dialysis independence in 20% patients (95% CI 12%–29%) after 5 years of ASCT.[10] A higher treatment related morbidity has been previously observed in this cohort but is gradually decreasing with advances in supportive care. Importantly, long-term survival in these patients is now noted to be independent of RI but depends on age and depth of response to therapy. The two largest published series have documented overall and progression-free survival similar to patients without RI.[3,10]

As better disease control is increasingly achieved in this cohort with a combination of induction with a novel agent and ASCT, it is important to consider sequential renal transplant in younger, medically fit patients. Durable improvement in renal function and survival can be achieved in this setting.[16,17]

The above data indicates that ASCT should not be withheld for any patient with myeloma based on the presence of RI. With appropriate precautions, comparable response rates and survival outcomes can be achieved in this cohort. The potential for dialysis independence make it an especially useful procedure in resource-limited settings.

Conflicts of Interest. None declared

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