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SUCCESSFUL AUTOLOGOUS STEM CELL TRANSPLANTATION IN A CASE OF MULTIPLE MYELOMA WITH MECHANICAL HEART VALVES

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ABSTRACT

Mechanical heart valve requires lifelong anticoagulation with vitamin K antagonists and targeted international normalized ratio (INR) of 2.5-3.5. Autologous stem cell transplantation (ASCT) is a procedure that typically results in low platelet counts. Mechanical heart valves necessitate anticoagulation therapy which increases the risk of hemorrhagic complications in patients undergoing ASCT. The combination of these factors highlights the need of adjusting anticoagulation dosage to prevent thrombosis or bleeding. Due to these complexities, some providers might consider the presence of mechanical heart valves as a reason to exclude a patient from ASCT. Herein, we present a case report of a patient with mechanical aortic and mitral heart valves, on anticoagulation therapy with warfarin who successfully underwent ASCT.

CASE

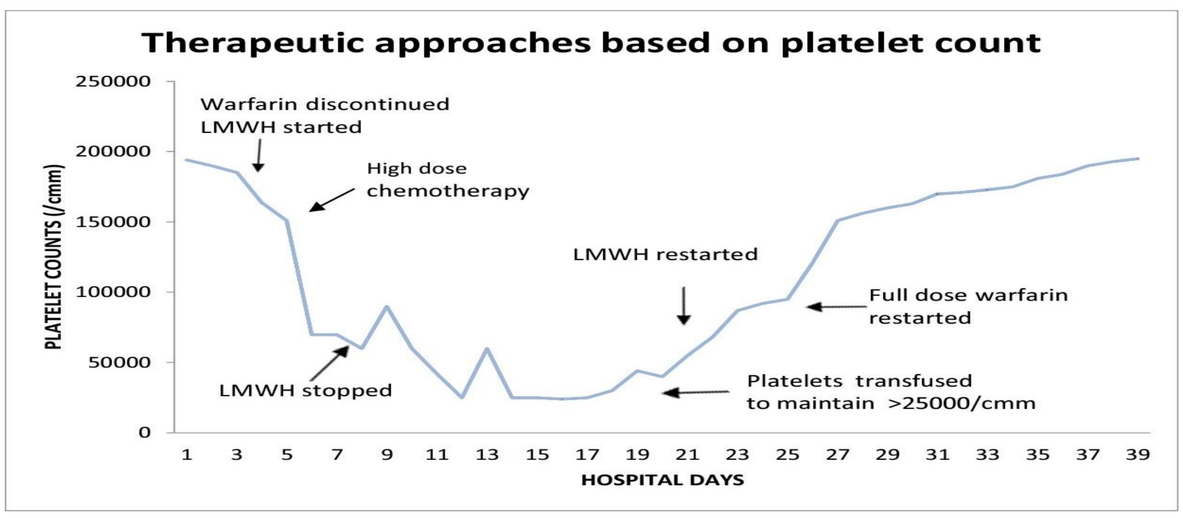
A 51 year old male presented to his orthopedician with complaints of lower back pain for 2 months. His past medical history revealed sterile bacterial endocarditis following which he underwent aortic and mitral valve replacement, with warfarin as an anticoagulation. His blood investigations revealed anemia (hemoglobin- 11.2 gm/dl). His renal and liver functions were within normal limits. Magnetic resonance imaging (MRI) of the lumbo-sacral spine revealed L1 (first lumbar) vertebral fracture with multiple bony lytic lesions in the multiple vertebrae. He underwent whole body positron emission tomography (PET) scan which revealed multiple lytic skeletal lesions involving left iliac, ischiopubic ramus, right femur, multiple dorsal and lumbar vertebrae with fracture of the L1 vertebra. Further evaluation included- serum free light chain (SFLC) analysis revealed free kappa chain of 16.16 mg/L and lambda chain of 3935.89 mg/L with a kappa/lambda (K/L) ratio of 0.004. Bone marrow biopsy confirmed the diagnosis of multiple myeloma with 26% of plasma cells by CD138 staining. Bone marrow cytogenetics (FISH) revealed standard risk cytogenetics. Serum protein electrophoresis (SPEP) revealed no M spike. His LDH and β-2 micro globulin were raised. He was diagnosed as multiple myeloma International staging system (ISS) stage-III.

He underwent induction chemotherapy with 5 cycles of D-VRd (Bortezomib 2 mg subcutaneously weekly, Lenalidomide 25 mg for 21 days out of 28 days cycle, Dexamethasone 40 mg weekly, Daratumumab 16 mg/kg per week as intravenous infusion for 8 weeks and then every 2 week for next 8 weeks) therapy with good symptomatic improvement. His repeat SFLC analysis revealed normal K/L ration, 0.88 (Kappa- 6.35 mg/L/ lambda chain of 7.2 mg/L). Bone marrow biopsy revealed no plasma cells and PET scan revealed complete metabolic response. Since patient had a complete response with induction therapy, he was counselled for consolidation with high dose melphalan followed by autologous stem cell transplantation (ASCT).

Stem cell mobilization was done with injection G-CSF(Granulocyte colony stimulating factor) for 5 days. In view of peripheral blood CD34 count <20/µL, he received injection plerixafor as part of the protocol (1) followed by stem cell harvest on day +5. A total of 5.1 X 10 ^{6}/kg CD34+ cells were collected and kept at 4 degree Celsius. High dose chemotherapy with melphalan at 140 mg/m2 was administered on day -1 followed by stem cell transfusion 24 hours later. He had neutrophil engraftment on day +9 and platelet engraftment on day + 13 post transplant.

Anticoagulation: After 3 days of stem cell mobilization, warfarin was discontinued and replaced with tablet aspirin and low molecular weight heparin (LMWH). In the post transplant period, platelet counts were monitored daily. LMWH and aspirin both were withheld after day 7 of stem cell transplant when his platelet counts reduced to <30,000/cmm. He was managed with single donor platelet (SDP) transfusion, to keep the basal platelet levels above 25,000/cmm at all times. Total 8 units of SDP transfusions were required. During recovery once the platelet counts were >50,000/cmm (day +15 post transplant) LMWH was restarted. Patient had persistent fever (day +3 to day +8 post transplant) and grade III of loose motions which was managed with empirical antibiotics. All the cultures were sterile. Warfarin (in the same as his previous dose) was resumed on day +18 post transplant when platelet counts were >90,000/cmm. By day 21 post transplant platelet counts returned to baseline. Though full recovery of platelet counts was achieved but with the same dose of warfarin as pre transplant his INR was ranging from 1.8 to 2.2 till day +30 post transplant, which required minimal increase in dosage of warfarin. INR in range of 2.5-3.5 was achieved on day +32 post transplant. Patient's leukocytes count reached a nadir on day 5 post transplant and engraftment was seen on day 9 post ASCT. His hemoglobin reached a nadir on day 7 at a value of 7.3 gm/dL and required 3 units of Packed red cells transfusions.

Post-transplant evaluation on day +100 revealed complete response, measurable residual disease (MRD) confirmed MRD negativity. Currently the patient is on maintenance therapy with capsule lenalidomide 10 mg daily for 21/28 days cycle. He also continues anticoagulation with warfarin for his mechanical aortic and mitral valves. Recent evaluation – patient continues to be asymptomatic and in CR.



DISCUSSION

The management of patients with mechanical heart valves undergoing autologous stem cell transplantation (ASCT) presents a unique challenge, as it requires careful balancing of anticoagulation therapy. Three major challenges we faced here were: prevention of infection, thrombosis and bleeding risk(2).

In patients undergoing ASCT, the treatment protocol typically involves antifungal, antiviral, and antibacterial prophylaxis. However, the use of warfarin for anticoagulation during this period raises concerns due to potential drug interactions, particularly with antifungal agents e.g. azoles – fluconazole/voriconazole and itraconazole, which are commonly used for prophylaxis. These interactions can lead to altered warfarin metabolism, increasing the risk of bleeding. As a result, in this case, warfarin was discontinued 2 days prior to high-dose chemotherapy and replaced with a combination of aspirin and low-molecular-weight heparin (LMWH). This switch was made for several reasons: ASCT requires a good peripheral line access, LMWH has a short half-life, eliminating the need for continuous monitoring of the international normalized ratio (INR). It is preferred in the post-transplant setting due to its predictable anticoagulant effect and ease of titration.

The patient's platelet counts were closely monitored daily to avoid bleeding complications(3). When platelet counts fell below 30,000/cmm, LMWH and aspirin were withheld to prevent bleeding risk. Single donor platelet (SDP) transfusions were administered to maintain platelet levels above 25,000/cmm, here we required more than usual SDP transfusions. Once the platelet count exceeded 50,000/cmm by day 15 without transfusion support, LMWH was reintroduced at a reduced dose and gradually increased to the full dose. This careful management allowed for a safe resumption of anticoagulation therapy while minimizing bleeding risks. When platelet counts reached more than 90,000/cmm, it was safe to restart warfarin. The patient's INR was closely monitored after the resumption of warfarin therapy. By day 32, the patient's INR was within the target therapeutic range (2.5-3.5) for anticoagulation, ensuring adequate protection against thrombotic events. It is important to note, a minimal increase in warfarin dose was required, achieving the target INR required careful titration, as the patient's platelet counts and other hematologic parameters continued to fluctuate during the post-transplant recovery phase.

Patient had fever for which we had to start him on empirical antibiotics as per in-house policy. Since patient had previous history of endocarditis, we closely monitored his cardiac parameters, including 2D echocardiography, close watch on vitals and cultures. Strict aseptic precautions were taken at all the times to prevent secondary infection. The complexities of managing anticoagulation in a patient with mechanical heart valves undergoing ASCT highlight the need for personalized and dynamic treatment regimens. The decision to transition from warfarin to LMWH and aspirin was based on the understanding that LMWH would allow for better management of the anticoagulation during a period of significant bone marrow suppression and unpredictable platelet recovery. Furthermore, careful monitoring of platelet counts and frequent adjustments in anticoagulation therapy are essential in ensuring a safe and effective recovery.

CONCLUSION

In conclusion, present case demonstrates that with careful management and individualized anticoagulation therapy, patients with mechanical heart valves can undergo ASCT safely, despite the challenges presented by anticoagulation therapy. The combination of LMWH for short-term anticoagulation during stem cell mobilization and transplant, followed by the careful reintroduction of warfarin, allowed for a successful outcome.

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