Abstract

Reactivation of cytomegalovirus (CMV) has been considered a rare consequence of autologous stem cell transplants (ASCTs). However, the recent introduction of novel chemotherapy agents has been associated with an increased incidence of viral infections. We present a case of CMV reactivation in a patient with multiple myeloma who received novel chemotherapy agents for induction prior to ASCT. The authors make suggestions aimed at decreasing mortality in similar patients.

Keywords: Cytomegalovirus reactivation; Multiple myeloma; Autologous stem cell transplant

Introduction

Cytomegalovirus (CMV) reactivation is a well-described complication of allogeneic stem cell transplants and recipients routinely receive prophylactic antiviral therapy. Historically, patients receiving autologous stem cell transplants (ASCTs) were considered low risk for CMV reactivation as the incidence of reactivation and disease is much lower following autologous transplantation than following allogeneic transplantation. However, the recent increased use of novel agents such as proteasome inhibitors and/or immunomodulators has led to an increased incidence in viral infections.

High-dose chemotherapy followed by autologous stem cell transplantation is a standard treatment for patients with multiple myeloma. The introduction of combination therapy with lenalidomide, bortezomib and dexamethasone (RVD) prior to ASCT has prolonged the progression-free survival (PFS) of multiple myeloma patients [1]. Recent studies suggest that this therapeutic regimen is associated with an increase in viral infections, including CMV reactivation [2]. We present a case of symptomatic CMV reactivation after RVD plus ASCT in a patient with multiple myeloma.

Case Report

A 47-year-old female, SS, with IgA kappa multiple myeloma, was treated with an ASCT in December 2017. Prior to the transplant, the patient received induction therapy with three cycles of RVD. During the first cycle, lenalidomide was discontinued due to the development of a rash and pomalidomide was started as an alternative immunomodulator. Prior to transplant, this patient was found to be seropositive for CMV based on the presence of CMV IgG antibodies. The same day the patient received the ASCT, she developed a pathologic right femur fracture from rolling in bed. Follow surgery for IM nail placement, SS suffered refractory hypotension thought to be caused by anecf or rocuronium although a fat embolism could not be excluded. She was admitted to the intensive care unit (ICU) for hypotensive shock and developed shock liver, hypoxic respiratory failure and acute kidney injury (AKI) due to hypotensive episodes.

Following a successful extubation, the patient returned to the hematology floor after 3 days in the medical ICU (MICU). The patient’s absolute neutrophil count returned to normal on D12+ but she was continued on filgrastim due to persistent fevers. At this time, empiric antibiotic coverage with vancomycin and meropenem was initiated and the infectious workup was negative. Clinically, SS had no symptoms, but her vitals remained hypotensive, febrile, tachycardic and tachypnic despite adequate oxygen saturation levels. When the patient began developing signs of respiratory distress, chest X-ray demonstrated multifocal pneumonia and pulmonary edema. IV fluids were stopped, but the patient’s rapidly declining respiratory function warranted admission to the ICU and intubation for septic shock and acute renal failure (ARF) on D17+. A CT thorax at this time was consistent with adult respiratory distress syndrome (ARDS). Sputum, urine and blood cultures, as well as cultures obtained with bronchoscopy, were all negative. The patient was continued on meropenem and vancomycin, and able to be extubated and transferred back to the hematology floor on D30+.

Once again, 7 days after discharge from the ICU, SS met the SIRS criteria with tachycardia, tachypnea, leukocytosis and fevers, despite another negative infectious work-up. During the patient’s 3-day stay in the MICU, she was started on aztreonam, linezolid, atovaquone and levoquine. Shortly after returning to the floor, the patient became febrile with rigors at D40+. CMV polymerase chain reaction (PCR) test indicated CMV viremia and the patient was started on valgancyclovir.

She became afebrile on valgancyclovir and was clinically stable so she was transferred to the inpatient rehabilitation floor.
Although a clinical response to therapy was evidenced, the patient’s CMV viral load continued to increase. After 2 weeks on valgancyclovir, she was switched to foscarnet, as it was suspected that valgancyclovir was contributing to worsening pancytopenia. CMV titers showed improvement from 17,640 to 14,490. SS became febrile again and was returned to the hematology floor, and was diagnosed with Clostridium difficile colitis and multifocal pneumonia in the setting of pulmonary edema. After 48 h, the patient was transferred back to MICU for refractory lactic acidosis. She unfortunately underwent cardiac arrest and expired 1 month after the diagnosis of CMV viremia.

Discussion

The use of proteasome inhibitors and immunomodulators for induction prior to ASCT, consolidation and maintenance after ASCT has improved PFS and overall survival (OS) in patients with multiple myeloma. A 2017 clinical trial found that patients who underwent ASCT and received RVD had a median PFS time of 50 months, compared to 36 months in patients that received RVD alone (P < 0.001). Furthermore, the RVD plus ASCT group had a higher complete response rate than the RVD-alone group. Albeit the overall survival (OS) was not statistically significant between groups, the authors of the study concluded that use of RVD with ASCT could lead to better outcomes for patients with multiple myeloma [1].

A recent meta-analysis found not only PFS benefit but also significant OS benefit in patients with newly diagnosed multiple myeloma receiving the immunomodulatory drug lenalidomide maintenance after ASCT [3]. In the lenalidomide maintenance group, median OS had not been reached at the median follow-up time of 79.5 months compared to a median OS of 86 months for the placebo or observation group (hazard ratio: 0.75; 95% CI: 0.63 - 0.90; P = 0.001). This study also demonstrates the utility of immunomodulators in different phases in the treatment of multiple myeloma including induction and maintenance.

CMV reactivation following an allogeneic bone marrow transplant in patients with multiple myeloma is much more common than after an autologous transplant, the incidences being 21-38% and 4-9%, respectively [4]. A 2013 study compared the use of novel agents, including bortezomib and/or immunomodulators, prior to ASCT with the conventional chemotherapy regimen used before transplant, consisting of vincristine, doxorubicin and dexamethasone (VAD). The results of this study showed a significantly higher incidence of CMV reactivation in patients who received the novel chemotherapy agents when compared to the conventional regimen. Further inquiry demonstrated that the patients who received bortezomib with or without immunomodulators had a higher incidence of CMV reactivation than the group receiving VAD (9.4% versus 1.1%; P = 0.019). This additional finding suggests that immunomodulators alone did not increase the incidence of CMV reactivation and that regimens with bortezomib prior to ASCT increase patients’ risk of CMV reactivation [2]. These results suggest that patients with multiple myeloma receiving novel agents should be routinely monitored for CMV reactivation to allow for timely diagnosis and treatment.

Based on the findings of the previously discussed studies, the patient in our reported case was at an increased risk of CMV reactivation since she received high-dose chemotherapy that included bortezomib before undergoing an ASCT for treatment of multiple myeloma. The patient’s high CMV viral load and resulting poor health status extended her hospital stay and ultimately contributed to her demise. We therefore suggest routine surveillance using CMV PCR in patients who are CMV IgG positive prior to RVD therapy and transplant would allow timely pre-emptive treatment with antiviral therapy against CMV leading to improved outcomes. Routine CMV surveillance with pre-emptive treatment would be a better option for these patients compared to administering CMV prophylaxis. Routine anti-CMV prophylactic antivirals are toxic and would likely not provide increased benefit when compared to the risk, especially given the low incidence of CMV reactivation. Although the incidence of CMV reactivation is low, the mortality is quite high, as in our patient, and instituting earlier antiviral treatments against CMV may be beneficial.

References