Journal of Clinical Virology 95 (2017) 36–41

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Full length article

Cytomegalovirus reactivation in lymphoma and myeloma patients undergoing autologous peripheral blood stem cell transplantation

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ARTICLE INFO

Keywords:
Myeloma
Lymphoma
Cytomegalovirus
Autologous stem cell transplantation

ABSTRACT

Background: Cytomegalovirus reactivation is often diagnosed in allogeneic hematopoietic cell transplant recipients and therefore could lead to CMV-related disease, involving many organs in these immunocompromised patients. In contrast, few studies investigated CMV reactivation and end-organ disease in patients undergoing Autologous Peripheral Blood Stem Cell Transplant (ASCT) since they are considered at low risk for both reactivation and disease.

Objectives: The primary outcome of the analysis was to understand the difference in incidence of CMV reactivation between MM and Lymphoma patients. Secondary outcomes included the difference between MM and Lymphoma patients when considering the effect of CMV reactivation on transplant related mortality (TRM) overall survival (OS) progression free survival (PFS), risk factors for reactivation, and median time to reactivation.

Study design: In this report, we retrospectively compared the incidence, risk factors, and outcome of CMV reactivation in adult patients with Myeloma (MM) and Lymphoma undergoing ASCT at the American university of Beirut Medical Center in Lebanon (AUBMC). A total of 324 consecutive ASCT were performed between January 2005 and March 2016. Serial weekly monitoring for CMV quantification was done using a quantitative PCR, starting from transplantation until the hospital discharge and afterwards based on the clinical symptoms in cases of clinical suspicion of reactivation after discharge from the hospital.

Results: The cumulative incidence of CMV reactivation was 16% (n = 53) with a median time of 16 (range, 4–242) days after ASCT. The incidence of reactivation was significantly higher in the MM (22%) and NHL (20%) groups, when compared to the HL (4%) (P = 0.001). There was a higher incidence of CMV reactivation according to age (≥50 vs ≤50 years) with higher incidence in the older population 24% vs 10% respectively (p = 0.0043). The mean time to CMV reactivation was significantly higher in the NHL group with a mean of 53.7 days when compared to the HL and MM groups with mean 19.75 days and 12.66 (range, 4–34) days respectively (P = 0.003). Twenty-two patients (76%) and three patients (75%) patients required specific antiviral therapy in the MM group and HL groups respectively; which was significantly higher (P < 0.001) then the NHL group with 13 (65%) patients requiring specific antiviral therapy.

Five patients (1.5%) developed CMV disease at a median of 60 days (range, 7–107) post ASCT: there was significant difference in the mean-time to reactivation based on disease type MM versus lymphoma 10 versus 33 days (P = 0.007).

In multivariate analysis, a higher age was associated with an increased risk of CMV reactivation; MM and NHL had higher risk of CMV reactivation when compared to HL, and progressive disease at transplant was associated with increased risk of CMV reactivation.

After a median follow-up of 21.5 months (range: 1–125), there was no significant impact on PFS, however there was significant decrease in OS of lymphoma patients who had CMV reactivation when compared to those

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http://dx.doi.org/10.1016/j.jcv.2017.08.006
Received 23 January 2017; Received in revised form 5 June 2017; Accepted 10 August 2017

without CMV reactivation (204 and 112 days respectively P = 0.045). TRM increased from 1.1% in patients with no CMV reactivation to 13% in patients with CMV reactivation (P = 0.003).
Conclusion: Our data suggests that CMV reactivation is not uncommon in ASCT recipients and may contribute to increase TRM. MM patients may have a higher incidence, of CMV reactivation with more anti-viral treatment requirements when compared to lymphoma patients, especially in older population.

1. Background

Autologous hematopoietic stem cell transplantation (ASCT) is accepted as a comparatively effective treatment to allogeneic HSCT (allo-SCT) for Multiple Myeloma (MM) and Lymphoma patients with the advantage of earlier engraftment [1,2]. In addition, ASCT patients do not usually develop a persistent immunodeficiency state which is common in allo-SCT patients who receive immunosuppressant drugs to prevent graft-versus-host disease (GVHD). Consequently, ASCT patients are generally thought to have less viral reactivation than allo-SCT recipients. However, the variety and frequency of viral reactivations in patients undergoing ASCT has not been adequately studied [3,4].

Cytomegalovirus reactivation is often diagnosed in allo-SCT recipients and could cause a CMV-related disease in these immunocompromised patients, involving many organs. Several studies have indicated that viral reactivation following allo-SCT is frequent, but viral reactivation after ASCT has not been thoroughly investigated [5,6]. Autograft recipients are generally considered to have low risk of CMV reactivation or end-organ disease. Without antiviral intervention, about 50% of patients with culture-proven CMV infection will develop CMV disease [7]. Preemptive anti-viral therapy has decreased the incidence of CMV disease in allo-SCT from 25 to 30% to less than 5% [8–10]. There are few reports of CMV infection/disease following ASCT, along with high rates of mortality primarily due to CMV pneumonia [11–14]. However, most of these data are from the era preceding the novel chemotherapeutic agents. In recent years, with changing chemotherapeutic regimens, available information is limited on the clinical progression and implications of CMV reactivation after ASCT. Frequent clinical manifestations of CMV disease are interstitial pneumonitis, gastrointestinal (GI) disease, hepatitis; retinitis, and encephalitis. Bone marrow suppression as a manifestation of CMV reactivation has also been described. The current diagnostic approach to CMV infection consists of sampling the peripheral blood for either CMV pp65 antigen (antigenemia assay) or polymerase chain reaction (PCR) [6,11,15].

Pre-emptive therapy with either Ganciclovir or Foscarnet is initiated in patients detected as positive [8].

2. Objectives

The primary outcome of the analysis was to understand the difference of CMV reactivation incidence between Lymphoma and Myeloma patients. Secondary outcomes included effect of CMV reactivation on transplant related mortality (TRM), overall survival (OS), progression free survival (PFS), risk factors for reactivation, and median time to reactivation (Fig. 1).

3. Study design

In this report, we retrospectively evaluated the difference between incidence, risk factors, and outcome CMV reactivation in adult Lymphoma and Myeloma patients undergoing ASCT in a major referral hospital in Lebanon. The study was approved by the institutional review board at AUBMC, and written informed consent in accordance with the declaration of Helsinki to review charts for research purposes is regularly obtained from patients prior to transplant at our center.

A total of 324 consecutive ASCT were performed for MM (41%) and lymphoma (59%) patients at the American University of Beirut Medical Center (AUBMC) between January 2005 and March 2016. None of our patients had CD34+ selection. All patients and transplant-related characteristics are listed in Table 1. CMV DNA viral load in blood was measured by quantitative polymerase chain reaction (PCR) in cases of clinical suspicion of reactivation.

3.1. Infection prophylaxis

Pneumocystis jiroveci prophylaxis included trimethoprim/sulfamethoxazole 20 mL suspension orally twice daily prior to transplantation, discontinued after morning dose on Day (−2) of transplant, and then resumed as soon as the absolute neutrophil count (ANC) exceeded 500/mm3. Levofloxacin 500 mg orally once daily was started when ANC was less than 1000/mm3 and discontinued when ANC was more than 1000/mm3 or fever protocol was activated regardless of ANC level. Doxycycline 100 mg orally twice daily was started from Day 0 after transplant until the removal of central IV catheter as a strategy to reduce central venous catheter infections. 24 Valgancyclovir 900 mg orally twice daily was started with conditioning and discontinued after morning dose on Day (−2) of transplant. Intravenous acyclovir or oral valacyclovir was used thereafter for Herpes simplex virus prophylaxis. Voriconazole 200 mg twice a day was used as a primary prophylaxis of fungal infections for all patients and started on Day (−1) of transplantation.

3.2. Definitions

CMV infection: is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen [16].

CMV disease: Histologically proven end-organ disease with CMV infection [16].

Death was attributed to CMV if there was evidence of autopsy proven organ damage by CMV.

CMV monitoring and treatment: Serial weekly monitoring for CMV quantification was done using a quantitative PCR assay with a sensitivity of 61 copies/ml and linear range 150–10,000,000 copies/ml (COBAS AMPLICOR and TAQMAN 48, assay from 2005 to 2009 and AMPLIPREP from 2009 to present time, Roche Diagnostics, New Jersey, USA) Monitoring was initially performed on a weekly basis, starting from transplantation until the hospital discharge and afterwards based on the clinical symptoms such as of fever, diarrhea, vomiting, and signs of bone marrow suppression, without evidence of bacterial, viral

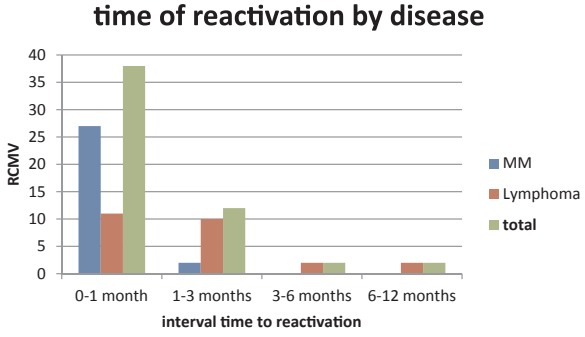

Fig. 1. Interval time for CMV reactivation post transplant.