Risk factors of Ganciclovir-related neutropenia after allogeneic stem cell transplantation: a retrospective monocentre study on 547 patients

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Abstract

Cytomegalovirus (CMV) infection is a serious complication that may occur in the weeks or months following bone marrow transplantation. However, both Ganciclovir and the CMV infection itself can cause marrow toxicity, notably neutropenia, that may consequently expose these immunosuppressed patients to life-threatening bacterial and/or fungal infections. The aim of this retrospective study was to identify factors associated with the occurrence of grade III–IV neutropenia among patients receiving pre-emptive Ganciclovir therapy after allogeneic stem cell transplantation at our Institution. We identified 547 consecutive patients transplanted from January 2005 to June 2011 at our Institution. In all, 190 patients (35%) presented with CMV reactivation of whom 30 patients (5%) were excluded from the analysis because they already had neutropenia at the time of reactivation. Finally, 160 (29%) patients were analysed. According to multivariate analysis, at the time of treatment initiation, the risk factors significantly associated with a grade III–IV Ganciclovir-related neutropenia included a high viral load (hazard ratio (HR) = 2.68, 95% CI 1.25–5.737, p 0.01); an absolute neutrophil count >3000 was a protective factor (HR = 0.26, 95% CI 0.125–0.545, p <0001) whereas serum creatinine >2 mg/dL was associated with higher Ganciclovir-related neutropenia (HR = 2.4, 95% CI 1.11–5.17, p 0.002). This large analysis revealed three risk factors for Ganciclovir-related neutropenia among patients with CMV reactivation after allogeneic stem cell transplantation; prompt identification of patients at risk when antiviral therapy is started may allow clinicians to adopt adequate preventive measures, so reducing the morbidity and mortality associated with CMV reactivation.

Keywords: allogeneic stem cell transplantation, cytomegalovirus, Gancyclovir, neutropenia
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Introduction

Cytomegalovirus (CMV) infection is a serious complication that may occur in the weeks or months following allogeneic stem cell transplantation (Allo-SCT) [1,2]. Therefore it must be treated as soon as positive CMV reactivation is noticed: pre-emptive therapy has been demonstrated to improve survival among patients reactivating CMV after transplantation [3,4]. However, Ganciclovir, as well as CMV infection itself, pose a well-known marrow toxicity risk, notably neutropenia, that may consequently expose these immunosuppressed patients to other life-threatening bacterial and fungal infections [5,6]. So far, only two studies have identified specific risk factors and outcome predictors for Ganciclovir-related neutropenia, finding low marrow cellularity between days 21 and 28, hyperbilirubinaemia >6 mg/dL during the first 20 days, serum creatinine >2 mg/L after day 21 and absolute neutrophil count to be predictive factors [7,8]. However, transplantation has evolved in recent years; especially because of the introduction of reduced-intensity conditioning regimens and supportive care [9,10]. The aim of the present analysis is to

identifying risk factors for neutropenia among a large cohort of patients treated with pre-emptive Ganciclovir who received Allo-SCT at our Institution over the last 6 years.

Patients and Methods

This is a retrospective study on a cohort of 547 consecutive patients receiving allotransplants from January 2005 to June 2011 at our Institution. Data collection was achieved by retrieval of electronic patient records. The study was approved by the Institut Paoli-Calmettes Institutional Board. Diagnoses were haematological malignancies, aplastic anaemia and metastatic solid tumours. Transplants were performed using three sources: bone marrow, peripheral blood stem cells and cord blood. Donors were HLA-matched siblings or matched or mismatched unrelated donors. Myeloablative, non-myeloablative and reduced-intensity conditioning regimens were administered according to local guidelines or established protocols [9,11,12].

GvHD prophylaxis and supportive care

Graft versus host disease (GvHD) prophylaxis consisted of cyclosporin A in 334 patients (61%), cyclosporin A + mycophenolate mofetyl in 198 patients (36%), 11 patients (2%) were free from any immunosuppressive therapy and mycophenolate mofetyl was used alone in four patients (1%). Cyclosporin A doses were adjusted to achieve blood levels between 150 and 250 ng/mL and to prevent renal dysfunction. Cyclosporin A was tapered starting on day 90 if no GvHD appeared. The main patient and transplant characteristics are shown in Table 1.

Our protocol for providing supportive care was the same throughout this time period. Prophylactic treatment against *Pneumocystis jirovecii* and toxoplasmosis consisted of trimethoprim-sulfamethoxazole (10 mg/kg/day trimethoprim) administered twice weekly. Patients also received daily oral amoxicillin (500 mg × 3/day) as prophylaxis against encapsulated bacteria and oral valacyclovir (500 mg × 2/day) as prophylaxis against herpes simplex virus.

CMV monitoring and treatment

Serial weekly monitoring for CMV quantification was done using either pp65 antigen (between 2000 and 2009) or a quantitative PCR assay on the whole blood (COBAS R, Roche Diagnostics, Branchburg, NJ, USA; with a lower detection limit of 30 copies/mL) (from 2009 to the present). Monitoring was performed weekly initially, starting from transplantation until day 90, and then every 4–8 weeks during the next 6 months. If there was evidence of reactivation (pp65 >2 cells/200 000 or PCR >1000 copies/mL), treatment was started with Ganciclovir (5 mg/kg intravenous twice daily) for 2 weeks, provided two consecutive PCRs performed 3 days apart became negative. If the PCR was still positive after 2 weeks of treatment, a maintenance therapy with Ganciclovir (5 mg/kg intravenously once per day) for another 14 days was proposed. CMV disease was diagnosed on demonstration of tissue invasion in biopsy specimens or demonstration of a positive CMV early antigen test on bronchoalveolar lavage, along with clinical and radiological features consistent with CMV. Only the first episode of CMV reactivation or CMV disease was taken into account.

Grade III neutropenia is defined by an absolute neutrophil count (ANC) between 500 and 1000/μL and a grade IV neutropenia by an ANC <500/μL. (Table 1).

Objectives and statistical analysis

The principal objective of the study was to identify factors associated with the occurrence of grade III–IV neutropenia among patients receiving antiviral therapy due to CMV reactivation. The following variables were analysed among patients with CMV reactivation: initial replicating virus copies (determined both by antigenaemia and PCR), time from transplant to CMV reactivation, patient's age, diagnosis, stem cell source, conditioning regimen, serum creatinine, hyperbilirubinaemia, absolute neutrophil count at CMV reactivation, presence of GvHD at CMV reactivation, relapse or progressive disease at CMV reactivation. These factors were then correlated with grade III–IV neutropenia during antiviral therapy. We considered values of PCR >5000 copies/mL and antigenaemia >10 infected cells as a high viral load, to be compared with lower values. Logistic regression was used both for univariate and multivariate analyses. Patients with grade III–IV neutropenia at the moment of CMV reactivation were excluded from this analysis. Variables with $p < 0.20$ were then included in the multivariate analysis; only factors with $p < 0.05$ were retained in the final model.

Secondarily, overall survival, transplant-related mortality (TRM) and relapse/progression were analysed and compared between patients who reactivated CMV versus those who did not. As CMV reactivation is a post-transplant event, landmark analysis was performed. Estimates of overall survival were calculated by the Kaplan–Meier method with respective 95% confidence intervals, starting from day of transplant. TRM, relapse/progression, CMV reactivation and grade III–IV neutropenia were evaluated by cumulative incidence; relapse/progression and TRM were considered competing events. Death from any cause was considered as a competing event in CMV reactivation and grade III–IV neutropenia analyses. The SPSS v16.0 and R v2.12.2 programs were used.