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Editorial

In the Era of New Drugs, Are Still Valid Guidelines of Cytomegalovirus Infection Monitoring in Autologous Hematopoietic Stem Cell Transplantation?

Cupelli L and de Fabritiis P*

Department of Hematology, St. Eugenio Hospital, Tor Vergata University, Italy

***Corresponding author:** de Fabritiis P, Department of Hematology, St. Eugenio Hospital, Piazzale Umanesimo 10, 00144 Rome, Italy

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Editorial

Cytomegalovirus (CMV) infects 50-90% of the adult population worldwide and is the most common infection in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) [1]. CMV reactivation is diagnosed in 80% of CMV seropositive patients and 30% of seronegative patients receiving grafts from seropositive donors. CMV reactivation, therefore, could progress to CMV-related disease, including pneumonia, hepatitis, colitis, encephalitis and bone marrow failure. Mortality of CMV pneumonia is about 60% [2]. The CMV sero-status of the donor-recipient pair, the source of hematopoietic stem cells, the "*ex vivo*" or "*in vivo*" T-cell depletion used in the haploidentical setting, the quality of the graft and the occurrence and treatment of graft-versus-host disease (GVHD) are the most important risk factors for early CMV reactivation [3-8]. Moreover, the multiple CMV reactivations in patients undergoing allogeneic HSCT increase the risk of late graft failure, affecting so negatively the transplant outcome that the donor CMV sero-status represents a crucial parameter during the unrelated donor search process [9].

Because of the high risk morbidity and mortality after CMV disease, guidelines recommend prospective monitoring of CMV viremia in allogeneic HSCT and pre-emptive anti-viral treatment to prevent progression from CMV reactivation to CMV disease [10]. In fact, detection of CMV in blood may predict the development of a CMV disease. CMV serology is an important risk factor to determine the risk for patient's CMV infection, although not suitable for the diagnosis of CMV disease. Methods used for CMV detection are based on determination of pp65 antigenemia and polymerase chain reaction (PCR). Quantitative real time PCR (QRT-PCR) is the most sensitive method for an early diagnosis, particularly in leukopenic patients [11]. In high risk patients, a prospective surveillance strategy for early detection of CMV reactivation is preferred to a clinically driven approach.

In autologous stem cell transplantation (ASCT), CMV reactivation is a rare event. Few studies investigate CMV reactivation and end-organ disease in patients undergoing ASCT, since they are considered at low risk for both reactivation and disease.

What can we learn from the "Conference on Infections in Leukemia (ECIL)?" Antiviral CMV prophylaxis, routine monitoring and pre-emptive therapy is not considered necessary in low risk patients because of the low likelihood of CMV disease and ASCT recipients belong to low risk group. There are, however, subgroups who are at risk for acquiring CMV disease, including those receiving CD34-selected graft, total body irradiation as part of conditioning regimen and previous treatments with alemtuzumab, fludarabine or 2-chlorodeoxyadenosine. These patients might potentially benefit from prospective monitoring and preemptive therapy [12].

Previous studies including CD34-positive selected autograft report an overall incidence of CMV infection of 26-39% [13]. Most of the patients undergoing ASCT are affected by Lymphomas or Multiple Myeloma. Over the last 15 years, innovative therapeutic agents have been available for Lymphoma and Myeloma treatments and most of the data concerning CMV infection in ASCT are from the era preceding the introduction of novel drugs, while scarce information are available on the impact of novel agents on clinical progression and implications of CMV reactivation after ASCT.

Have the new drugs an impact on CMV reactivation rates in Myeloma and Lymphoma patients undergoing ASCT? Is it time to change our approach on CMV surveillance after ASCT?

Several publications confirmed that the highest risk for CMV reactivation is among patients with lymphoproliferative diseases. The rate of CMV reactivation in different reports is ranging from 10% to 40% according to different diagnostic strategies. In fact, the incidence of CMV infection in hematologic patients undergoing ASCT may range from 17% to 33% when a prospective monitoring is adopted and from 3% to 13% with a clinical driven strategy [14]. Progression from CMV reactivation to CMV disease is still a rare event, with an incidence of CMV pneumonia of 2-9% evolving into fatal disease in a high proportion of cases [15].

The introduction of Rituximab and other monoclonal antibodies in the treatment of non-Hodgkin's lymphoma or the immune-modulators and proteasome inhibitors in the treatment of multiple myeloma (MM) favored the occurrence of new complications, including viral infections; the recent use of monoclonal antibodies during induction chemotherapy or as a part of conditioning regimen caused an increase of CMV infections also after ASCT [16]. Jain et al analyzed the results of CMV PCR in ASCT recipients, 24% of those treated with Rituximab, indicating less than 3% of CMV PCR positivity. The Authors concluded that, despite prior publications based on limited data, Rituximab does not appear to contribute to an increased frequency of symptomatic CMV reactivation following ASCT [17]. Recently, Massoud, et al. analyzed 324 Lymphoma and

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Myeloma patients undergoing ASCT from 2005 to 2016 in their centre. The primary outcome was to demonstrate whether a difference in CMV reactivation between Lymphoma and Myeloma patients might be present after ASCT. They used a prospective surveillance until hospital discharge and a clinical driven approach after patients discharge. The global incidence of CMV reactivation was 16% and the incidence of CMV disease 1.5%. Older age and Multiple Myeloma were associated with more reactivation and higher incidence of CMV infection, respectively, with no difference in overall survival and progression free survival both in Lymphoma and Myeloma patients. In total, four patients died for CMV disease [18].

Could the novel anti-myeloma drugs used as induction therapy before ASCT be responsible of these results? Although the question is still unsolved, the hypothesis might be not far from its demonstration. More questionable is the necessity of CMV surveillance for patients with low reactivation risk in an ASCT setting. Kaya, et al observed 37%, 6.8% and 1.2% of CMV reactivation, requirement for pre-emptive therapy and CMV disease, respectively [19] and a report from the Rome Transplant Network (RTN) indicated a higher risk of CMV reactivation in patients with Multiple Myeloma treated with Bortezomib based regimens, probably for an increase of CMV screening in patients receiving Bortezomib [20].

Additional advances in MM treatment had a positive impact on both disease-free and overall survival. These advances include the use of novel agents (e.g., proteasome inhibitors, immune-modulators and monoclonal antibodies), as well as more intensive transplantation regimens that involve two sequential ASCTs (i.e., tandem transplantation). These treatments also result in a deeper immune-suppression, which increases susceptibility to opportunistic infections. The cumulative immune-suppression in Myeloma patients is the result of the combined effect of high dose corticosteroids, a chronic disease in the elderly and the addition of proteasome inhibitors. Bortezomib is an inhibitor of the 26S proteasome used as first line and for relapse in multiple myeloma; as a powerful immune-suppressive agent it diminishes the proliferation and function of CD8+, CD4+ T lymphocytes and NK cells. After treatment with Bortezomib an increased incidence of infection from herpes viruses has been reported [21].

The necessity of a routine monitoring for ASCT recipients such as patients undergoing allogeneic HSCT remains an open question: Massoud does not recommend a prospective surveillance [18]; Kaya suggests CMV surveillance in areas with high prevalence of CMV seropositivity [19]. It seems reasonable that the risk factors for CMV screening after ASCT must be re-defined in the era of the novel agents.

The analysis of the last 20 years does not demonstrate a clear increase in CMV reactivation or infection and if Rituximab treatment before and during stem cell transplantation does not seem to have an impact on CMV infection, Bortezomib and the newer innovative agents may play a greater role on increasing the CMV reactivation in Myeloma patients, although these data have to be confirmed in prospective studies.

Is it time to recommend a prospective CMV monitoring in patients undergoing ASCT? Probably not yet. A clinically driven approach does not seem to have a detrimental effect on transplant outcome. Furthermore, it would be more cost effective. On the other hand, it is important to remember that CMV end-organ disease is a serious complication also in ASCT patients, with a mortality similar to that observed in patients undergoing allogeneic HSCT. Through a review of the recent literature, though accurate, does not help much: most of the studies published in the last years are retrospective, often from single centre; it is difficult to compare different studies because of different strategy (prospective surveillance vs. clinically driven approach) or duration of CMV monitoring, different diagnostic tests (determination of pp65 antigenemia, viral DNA or mRNA), and different threshold to start anti-viral treatment.

Some patients with low viral load can clear CMV from the blood without therapy, as well as cases of CMV disease without prior CMV viremia. In general, CMV disease and mortality are similar irrespective to the diagnostic strategy adopted.

In the next years newer drugs may have even a greater impact on CMV disease in ASCT recipients; we need prospective studies with large numbers of patients to answer these questions and keep up the pace of rapid changes that are radically mutating the therapies of hematologic malignancies.

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