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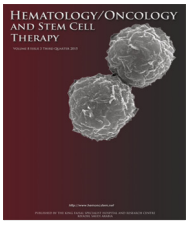

REVIEW ARTICLE

Emerging concepts in cytomegalovirus infection following hematopoietic stem cell transplantation

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Abstract
Despite the refinements in molecular methods for the detection of cytomegalovirus (CMV) and the advent of highly effective preemptive strategies, CMV remains a leading cause of morbidity and mortality in hematopoietic cell transplant (HCT) recipients. CMV can cause tissue-invasive disease including pneumonia, hepatitis, colitis, retinitis, and encephalitis. Mortality in HCT recipients with CMV disease can be as high as 60%. CMV infection has been associated with increased risk of secondary bacterial and fungal infections, increased risk of graft-versus-host disease, and high rates of non-relapse mortality following HCT. The risk of CMV is highly dependent on the donor (D) and the recipient (R) serostatus ($D^-/R^+ > D^+/R^+ > D^+/R^- > D^-/R^-$). Among allogeneic HCT recipients, high-dose corticosteroids, T-cell depletion, graft-versus-host disease, and mismatched or unrelated donors constitute the main predisposing factors. However, not all seropositive individuals with these risk factors develop CMV, which strongly suggests that host factors, such as those regulating CMV-specific T-cell responses, play a major role in predisposition to CMV in HCT recipients. Here, we discuss emerging concepts in CMV infection in HCT with emphasis on immunological factors that govern CMV reactivation and the applicability of immune monitoring to understand correlates of pathogenesis and its potential to guide clinical decision making.

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Introduction

Human herpesvirus 5, better known as cytomegalovirus (CMV), infects 50–90% of the adult population worldwide, and is the most common opportunistic infection in allogeneic hematopoietic cell transplant (HCT) recipients, causing significant morbidity and mortality [1–5]. The CMV genome is the largest among known human viruses (~230 kb), containing 200 genes encoding proteins [1]. Without prophylaxis, CMV reactivation occurs in up to 80% of CMV-seropositive and 30% of CMV-seronegative HCT recipients receiving grafts from seropositive donors [5].

Risk factors for CMV reactivation

CMV seropositivity and reactivation are associated with adverse outcomes following HCT [6–10]. Donor and recipient serostatus is the primary risk factor for CMV reactivation. CMV reactivation is rare after autologous transplantation, except in the setting of T-cell depletion. Risk is highest among seropositive allogeneic HCT recipients (R^+) who receive grafts from seronegative donors (D^-; lacking CMV immunity) and almost null in seronegative recipients (R^-) from seronegative donors who receive leukoreduced blood products. In 928 HCT patients who received cyclosporine/methotrexate/antithymocyte globulin graft-versus-host disease (GVHD) prophylaxis, D^-/R^+ patients had a substantially lower survival than D^+/R^+ patients [11]. Survival rates were also lower for D^-/R^+ HLA-matched sibling recipients compared with D^+/R^+ HLA-matched unrelated donor transplant recipients, demonstrating the significance of donor serostatus. Key risk factors for early reactivation include high-dose corticosteroids, *ex vivo* or *in vivo* T-cell depletion, GVHD, and mismatched or unrelated donors [5].

In a single-institution study of 269 consecutive allogeneic HCT recipients, we observed a surprisingly high cumulative incidence of late CMV reactivation of 31% [12]. Late CMV reactivation was strongly associated with antecedent early reactivation (occurring in 45% of those with early reactivation vs. 16% of others). Significant risk factors for late reactivation in multivariate analyses were GVHD, donor type, use of a CMV-seronegative donor, and lymphoid malignancy. Cord blood transplant recipients and recipients of T-cell depleted grafts also have high risk of CMV reactivation and disease [13]. However, even in the absence of antiviral prophylaxis, not all individuals with such risk factors develop reactivation, suggesting host factors unique to each recipient that influence the risk of progression to uncontrolled viremia.

The burden of CMV in HCT

CMV disease may include pneumonia, hepatitis, colitis, retinitis, and encephalitis [2,5,14,15]. Mortality of CMV pneumonitis after HCT may approach 60% [14,15] and is only slightly lower in the modern era [16]. CMV reactivation is associated with increased risk of secondary bacterial and fungal infections [17,18]. A recent Center for International Blood and Marrow Transplant Research study of 9469 stem cell transplant recipients transplanted between 2003 and 2010 suggested CMV reactivation remains associated with poor post-transplant outcomes, especially non-relapse mortality (NRM), in the modern era [10].

Recently, Boeckh and colleagues reported an association between a CMV viral load ≥250 IU/mL and increased risk of early post-HCT mortality [19]. At our center we observed NRM rates close to 56%, 78%, and 100% at 100 days, 200 days, and 365 days post-HCT, respectively, among patients failing to eradicate CMV viremia despite antiviral therapy and reduction of immunosuppression [20]. Most deaths were attributed to bacterial and invasive fungal infection, consistent with the fact that CMV disease is an independent risk factor for aspergillosis (adjusted hazard ratio 7.0) [17,21,22] and candidemia (adjusted relative risk 16.4) [23]. Nichols et al. [18] reported higher mortality due to bacteremia or invasive fungal infection among CMV D^+/R^- (18.3%) than D^-/R^- (9.7%) patients. Similarly, each week of ganciclovir treatment is associated with 1.4-fold increase in the risk of invasive aspergillosis [22].

Tackling CMV disease

Unfortunately, there has been little progress in CMV prophylaxis or therapy in the last 15 years. Only four antiviral drugs are approved by the US Food and Drug Administration for CMV prophylaxis or therapy: Ganciclovir (1989), foscarnet (1991), cidofovir (1996), and the prodrug valganciclovir (2001). In a recent randomized trial, valganciclovir prophylaxis performed similarly in reducing the composite endpoint of late CMV disease, invasive bacterial or fungal disease, or death when compared with polymerase chain reaction (PCR)-guided pre-emptive therapy [24]. However, given toxicities common to approved anti-CMV therapies, especially myelotoxicity and nephrotoxicity, pre-emptive therapy remains the standard of care [1,3,5].

Monitoring frequency (typically once or twice weekly), duration (typically 100–200 days), and treatment threshold for pre-emptive therapy vary widely [2,6,12,25–35]. Of note, the method of testing for CMV reactivation, quantitative viral load, and type of treatment received for CMV reactivation are not reported to the Center for International Blood and Marrow Transplant Research [10].

In a large HCT cohort, a lower treatment threshold (≥25 IU/mL) in patients at greater risk of rapid CMV replication (e.g., T-depleted or steroid-treated recipients) improved pre-emptive treatment success [27]. Recently, Tan et al. [34] suggested that preemptive therapy should be started with low-level viremia (135 IU/mL) but also acknowledged that this may unnecessarily treat viremia that might resolve spontaneously. Although, the salutatory effects of early antiviral therapy must be balanced against the risk of drug-related toxicity due to overtreatment, recent studies suggest that early initiation of pre-emptive therapy is actually associated with shorter duration of viremia and reduced antiviral exposure [20,30,34].

CMV resistance has been increasingly recognized and may be caused by mutations targeting the UL54 DNA polymerase and the UL97 kinase. Resistance should be suspected when CMV viremia fails to improve or increases after 2 weeks of appropriately dosed and delivered antiviral therapy. The full potential of novel therapies such as maribavir [36–

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