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Review

Risk Factors for Cytomegalovirus Infection After Allogeneic Hematopoietic Cell Transplantation in Malignancies: Proposal for Classification

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Abstract. *Aim: To identify and classify risk factors for cytomegalovirus (CMV) infection and disease in patients receiving allogeneic hematopoietic stem cell transplantation (allo-HSCT), treated mainly for acute leukemia. Materials and Methods: A literature search was performed;eligible trials were clinical studies assessing the risk factors for CMV infection or disease in multivariate analysis. Results: Early reactivation in the setting of allo-HSCT took place mainly in patients without CMV prophylaxis, while late reactivation mainly in those patients who had completed previous prophylaxis or were on anti-CMV strategy based on pre-emptive prophylaxis. We propose classifying risk factors for CMV reactivation and CMV disease in patients after allo-HSCT as major and minor ones. Three major risk factors for CMV reactivation and CMV disease were found: (i) CMV-negative donor CMV-positive recipient serostatus, (ii) acute or chronic graft-versus-host disease, and (iii) unrelated or mismatched donor. Conclusion: CMV reactivation should be regarded as a continuous function of recipient and donor CMV-seropositivity and recipient immune suppression, caused by conditioning, immunosuppressive therapy and human leukocyte antigen disparity between donor and recipient.*

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Cytomegalovirus (CMV), classified as the beta human herpesvirus type 5 (HHV-5), is widespread around the world. Primary CMV infection always progresses to long-life latency (1). In the case of immune suppression, latent infection may be reactivated, causing direct and indirect adverse effects in the affected patient. The highest degree of immune suppression is regarded to occur in patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT), solid organ transplantation and during chemotherapy for leukemia (2-4). In an immunosuppressed host, CMV reactivation can be a significant cause of morbidity and mortality, especially in patients after transplantation (2, 5) or malignancy (6, 7).

The objective of this study was to identify and classify risk factors for CMV reactivation and CMV disease in patients after allo-HSCT.

PubMed Library from 1995 to August 2017 was searched using the terms: CMV, risk factor, hematopoietic stem cell transplantation, and multivariate analysis. A total of 108 publications were found. After exclusion of not pertinent, non-English and review papers, 30 potentially relevant papers were selected. Sufficient data available for further analysis of the role of risk factors for CMV infection and diseases were found in 10 articles (listed in Tables I and II). Definitions of CMV infections, reactivation, disease, and types of therapy were published elsewhere (8, 9).

CMV infection in patients after HSCT. CMV seropositivity is a function of gender and age. The risk of CMV seropositivity is a continuous variable and increases with age both in men and women, however it is slightly more pronounced in females. The CMV positivity in the overall population varies from about 30% in childhood up to 60-70% in the sixth decade of life (10). The reactivation of

CMV is related to immunological status of the host. Reconstitution of CMV-specific cellular immunity post-HSCT is a critical determinant of the control of CMV infection. Since T-cell-mediated cellular immunity is the most important factor in controlling CMV replication (11), a delayed recovery or lack of CMV-specific $CD4^+$ and $CD8^+$ cells is associated with late CMV disease and death in patients who have undergone HSCT (12).

CMV is an important cause of morbidity and mortality after allo-HSCT. CMV causes various end-organ diseases in susceptible patients, can cause graft failure, increases the risk of acute or chronic graft-*versus*-host disease (GVHD), enhances invasive fungal infection, contributes to graft failure and contributes to fatal outcome. The most frequent clinical manifestations of CMV disease in immunosuppressed patients are: pneumonia, hepatitis, bone marrow suppression, retinitis and gut infection. The potential reasons for CMV adversely affecting transplant outcomes include (i) increased risk for bacterial and fungal co-infections, (ii) increased organ toxicity directly via CMV infection itself and indirectly via associated side-effects of antiviral therapy, and (iii) increased incidence and severity in GVHD (5).

Possible risk factors for CMV reactivation and disease. Recent data indicate that an incidence of CMV reactivation patients after HSCT is about 30% (2, 5, 13). The rate of CMV disease decreased from 18-27% in 1995-2000 (14) to approximately 1.4-10% in various studies of patients undergoing HSCT (15-17). The median time to CMV reactivation ranged between 27-46 day post-transplant, regardless of serological status of the donor and recipient (5, 17-19), while the median time to development of CMV disease was 104 (range=39-200) days (17). Antiviral prophylaxis may delay the reconstitution of the CMV-specific T-cell lymphocytes, which may increase the risk of the development of CMV reactivation late (>100 days) after transplantation (20,21).

Reactivation of CMV infection in patients after HSCT is influenced by a number of risk factors including those related to the recipient (CMV serostatus, age, sex), donor (CMV serostatus and match, age, sex, type of donor, human leukocyte antigen (HLA) match, stem cell source), transplant (intensity of conditioning, type of conditioning, T-cell depletion), immunosuppressive treatment (prophylaxis, occurrence and treatment for acute or chronic GVHD, specific immuno-suppressive drugs used in prophylaxis and therapy), and immune recovery after HSCT (speed of immune, recovery of CMV-specific cytotoxic T-lymphocytes). CMV reactivation in patients after allo-HSCT occurs in early or late post-transplant phase. Early reactivation takes place mainly in patients without CMV prophylaxis, while late reactivation mainly in those patients who had completed previous prophylaxis or were on an anti-CMV strategy based on pre-emptive treatment.

*Risk factors for CMV reactivation. CMV donor and recipient (D/R) serology: I*n allogeneic HSCT recipients, the most important risk factor for CMV disease seems to be the serological status of the donor and recipient. CMV-seronegative patients receiving stem cells from a CMV-seronegative donor (D−/R−) have a very low risk of primary infection if CMV-safe blood products are used (11). The largest recent studies, including over 26,000 patients in total, have shown reactivation rates of 32-33% for D−/R+, 28-32% for D+/R+, 9-11% for D+/R−, and 2-4% for D−/R− (2, 5). A relatively higher prevalence of CMV reactivation and the development of CMV infection in D−/R+ patients compared to D+/R+ has been shown in several large studies (2, 18, 22) (Table I). The rationale for this phenomenon is based on two factors related to donor and recipient CMV serostatus that influence CMV response in patients immediately after allo-HSCT: antiviral cytokines and CMV-specific T-cells. With respect to cytokines, R+ recipients receiving grafts from D− individuals reconstituted fewer multifunctional $CD8^+$ T-cells expressing the antiviral cytokines tumor necrosis factor-α (TNF-α), interferon-χ (IFN-χ), chemokine macrophage inflammatory protein-1β (MIP-1β), and degranulation marker CD107 compared with D+/R+ transplants. The relative lack of multifunctional $CD8^+$ T-cells persisted until at least 1 year post-HSCT (18). Because D+/R+ transplants, on average, generated higher levels of multifunctional CMV-specific T-cells compared with D−/R+ HSCT recipients, the benefit of donor points for CMV-positive recipients is obvious (18). The frequency of CMV-specific T-cells in CMV-positive patients receiving transplants from CMV-negative donors is very low in comparison to patients receiving transplants from CMV-positive donors (22).

Conditioning: The risk of CMV reactivation was higher after myeloblative than reduced-intensity conditioning (RIC) in two studies (14, 23). The use of total body irradiation was found to be risk factor for CMV reactivation in one study from 2001 (24). RIC is less toxic and results in initial establishment of mixed T-cell chimerism, with prolonged presence of host T-cell immunity (14). This is why RIC-HSCT was associated with a lower risk of high-grade CMV infection, while increased risk of late CMV disease after RIC-HSCT was pronounced during the earlier years, but not detectable in more recent periods. These results suggest that residual host cells after RIC-HSCT reduce progression to a higher CMV viral load in RIC-HSCT recipients; however, this effect does not appear to protect against serious complications of CMV. Therefore, CMV prevention strategies in RIC-HSCT recipients should be similar to those used in myeloblative -HSCT recipients (14).

Type of donor: In most studies, the risk of CMV reactivation was higher after unrelated or mismatched donor than after matched sibling donor (MSD) HSCT (14, 19, 23, 25). These results are not unequivocal for development of CMV disease (14, 17, 26).

Table I. *Summary of risk factors analyses for cytomegalovirus (CMV) reactivation in multivariate analyses.*

Author, year (Ref)	CMV serostatus			Source	RIC	Age	UD/MMD	aGVHD	Year	Race	Other
	D−/R+	D+/R+	D+/R−								
Takenaka *et al*., 2015 (19) (n=3539)	Yes (HR=2.15, $p<0.01$)	Yes (HR=1.92, $p<0.01$)	No	No	No	>50 Years (HR=1.40, $p<0.01$)	Yes (HR=1.38, $p=0.01$)	Yes (HR=2.35, $p<0.01$)			
Nakamae *et al*., 2009 (14) (n=3026)	Yes (HR=1.4, $p<0.01$)		No; Incidence= 0.15		Yes (HR=0.7, $p<0.001$)	>41 Years (HR=1.5, $p<0.001$)	Yes (HR=1.6, $p=0.04$)	Yes (HR=1.8, $p<0.001$)	>2003 (HR=0.4, $p<0.001$)	Non-Caucasian (HR=1.4, $p<0.01$)	HSV1 (R+) (HR=0.6, $p<0.001$)
Zhou *et al*., 2009 (18) (n=375)	Yes (HR=1.8, $p=0.009$)							Yes (HR=2.1, $p=0.001$)			
Walker *et al*., 2007 (27) (n=753)	Yes (HR=14.5, $p<0.01$)	Yes (HR=12.0, $p<0.01$)	No	No		>18 Years (HR=1.4, $p=0.05$)		Yes (HR=2.5, $p<0.01$)			TCD (HR=2.2, $p<0.01$)
Marty *et al*., 2007 (23) (n=606)	Yes (HR=51.1, $p<0.001$)	Yes (HR=37.6, $p<0.001$)	Yes (HR=5.3, $p=0.02$)	No	Yes (HR=0.4, $p=0.036$)	No	MMD (HR=1.9, $p=0.06$)	Yes (HR=1.7, $p=0.016$)	No	No	SRL (HR=0.22, $p=0.001$)
Lin *et al*., 2002 (25) (n=124)	Yes (HR=54.1, $p<0.001$)			PBSC (MSD only) (HR=10, $p=0.005$)		No	Yes (HR=5.4, $p=0.03$)	Yes (HR=nd, $p=0.04$)			
Nichols *et al*., 2001 (24) (n=119)	Yes (only univariate)				TBI (HR=2.6, $p=0.04$)		Yes (only univariate)				Steroids ≥2 mg/kg (HR=10.0, $p=0.001$)
Ozdemir *et al*., 2007 (21) (n=269) (late reactivation)	Yes (HR=2.0. $p=0.03$)						Yes (HR=3.4, $p=0.01$)	Yes (MSD) (HR=2.9, $p=0.003$)			cGVHD (MSD) (HR=8, $p=0.006$), lympho-penia at D+100 (HR=2.0, $p=0.025$), early CMV >2 reactivations (HR=7.1, $p<0.001$)

HR: Hazard ratio; R: recipient; D: donor; RIC: reduced-intensity conditioning; MSD: matched sibling donor; UD: unrelated donor; MMD: mismatched donor; aGVHD: acute graft-*versus*-host disease; cGVHD: chronic GVHD; HSV1: herpes simplex virus 1; nd: not determined; TCD: T-cell depletion; SRL: sirolimus use in prophylaxis GVHD; TBI: total body irradiation; PBSC: peripheral blood stem cells.

Stem cell source: In the only study comparing the impact of three stem cell sources on CMV reactivation, no significant differences were found (27). In one study, statistical significance was found, however, only for MSD transplants (25).

GVHD: Acute or chronic GVHD is the risk factor for CMV reactivation and disease in virtually all studies, both for early and late reactivation, regardless of therapy used and type of donor.

Late reactivation: In an analysis of factors affecting late CMV reactivation, three groups of patients at risk were determined. The high-risk group included patients who did not receive a MSD graft or developed GVHD despite receiving MSD graft, and had more than two episodes of early CMV reactivation and either one (or both) of two additional risk factors: (i) lymphopenia post transplant day 100 and (ii) transplantation from a CMV-seronegative donor. The low-risk patients were those without antecedent early reactivation, those with early reactivation and transplanted for a myeloid malignancy from a MSD donor without subsequent acute GVHD. The intermediate-risk group

Table II. *Summary of risk factors analyses for cytomegalovirus (CMV) disease in multivariate analyses.*

Author, year (Ref)	CMV serostatus D−/R+	Donor gender	UD/MMD	a/cGVHD	DNA-emia	Other
Nakamae *et al*., 2009 (14) (n=3026)	Yes (HR=1.4 $p<0.01$)	F→M (HR=1.4 $p=0.02$)	No	Yes (HR=2.1 $p<0.001$	>1000 c/ml (HR=3.7 $p<0.001$)	HSV1 (R+) (HR=2.3 $p=0.01$)
Ljungman *et al*., 2006 (17) (n=162)	Yes (HR=5.4 $p=0.049$)		No	Yes (HR=9.7 $p=0.006$)	No	ATG No
Ljungman *et al*., 1998 (26) (n=594)	Yes (R+) (HR=5.0 $p=0.04$)		Yes (HR=2.6 $p=0.005$)			Age (per year) (HR=1.02, $p=0.018$) Pre-emptive (PCR) (HR=0.4, $p=0.008$)

HR: Hazard ratio; R: recipient; D: donor; MSD: matched sibling donor; UD: unrelated donor; MMD: mismatched donor; F: female; M: male; a/cGVHD: acute/chronic GVHD; ATG: anti-thymocyte globulin; PCR: polymerase chain reaction; HSV1: herpes simplex virus 1.

Table III. *Classification of risk factors for cytomegalovirus (CMV) reactivation and disease.*

Risk factors	CMV reactivation	CMV disease
Major	• D−/R+ CMV serostatus • Acute/chronic GVHD • UD/MMD	• D−/R+ CMV serostatus • Acute/chronic GVHD • UD/MMD
Minor	• D+/R+ CMV serostatus • Age (over 40-50 years) • Myeloablative conditioning • Lymphopenia <900 cells/μL at day +100 • T-cell depletion	• D+/R+ CMV serostatus • High viral load

D: Donor; R: recipient; GVHD: graft-*versus*-host disease; UD: unrelated donor; MMD: mismatched donor.

included patients who did not fit into either the low- or high-risk groups (21).

Protective effect of sirolimus: Sirolimus-based immunosuppressive regimens reduced the cumulative incidence of CMV disease in HSCT recipients in one study (23). Sirolimus has antiproliferative properties and probably inhibits the kinetics of CMV replication (28,29).

Risk factors of CMV disease in patients after allo-HSCT. Recipient and donor serostatus also play a key role in the development of CMV diseases after HSCT (26). Patients who received unrelated or mismatched family donor transplants had increased risks for CMV disease, CMV-associated death, and treatment-related mortality (TRM). Age was a significant risk factor for CMV disease and TRM, being the continuous variable, and the risk increased with age. In addition, patients who received mismatched or unrelated donor transplants had increased risk for CMV disease, death in CMV disease, and TRM (26). High CMV viral load was a risk factor for development of CMV disease in two studies (14,30). The summary of results presented in analyzed studies is shown in Table II.

Classification of risk factors for CMV reactivation and CMV disease. We propose to classify risk factors as major or minor with respect to their significance in majority of studies with multivariate analyses: major risk factor, when confirmed in at least half of the studies for CMV reactivation; and minor risk factor, when confirmed more than once or very well evidenced and clinically important.

Three major risk factors for CMV reactivation were determined: D−/R+ CMV serostatus, acute or chronic GVHD (with concomitant immunosuppressive therapy), and unrelated or mismatched stem cell donor. The same three factors were significant for CMV disease (Table III). Minor risk factors for CMV reactivation included: D+/R+ CMV serostatus, age, myeloablative conditioning, and lymphopenia <900 cells/μl at day +100. Age, in general, was regarded as a continuous variable, with increasing age being the risk factor for CMV reactivation, and in two studies the

threshold age of 40 or 50 years was specified. Minor risk factors for CMV disease included: D+/R+ CMV serostatus, and high viral load, while intensity of conditioning had no impact. The use of steroids itself can be regarded as a risk factor, however, it was found to be strictly related to treatment of acute or chronic GVHD, thus it is not a fully independent risk factor. The adverse role of the use of anti-thymocyte globulin or sex mismatch between the donor and recipient was not well proven.

Two protective factors were determined: the use of sirolimus in GVHD prophylaxis reduced the incidence of CMV reactivation (23), and the use of pre-emptive treatment reduced the incidence of CMV disease (26).

In conclusion, CMV reactivation should be regarded as a continuous function of recipient/donor CMV-seropositivity and immune suppression, caused by conditioning, immunosuppressive treatment and HLA disparity. D−/R+ CMV serostatus, acute or chronic GVHD, and unrelated or mismatched stem cell donor are the major risk factors for CMV reactivation and disease after allo-HSCT.

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