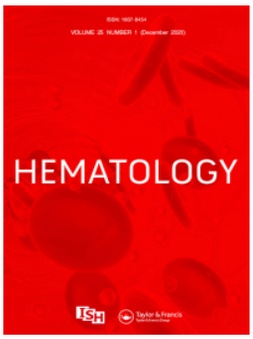

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# Cytomegalovirus immunoglobulin serology prevalence in patients with newly diagnosed multiple myeloma treated within the GMMG-MM5 phase III trial

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**ABSTRACT**

**Objectives:** The seroprevalence of antibodies against Cytomegalovirus (CMV) is an established poor prognostic factor for patients receiving an allogeneic stem cell transplantation. However, the impact of CMV serology on outcome after autologous stem cell transplantation remains unknown.

**Methods:** Here, we analyzed the CMV immunoglobulin (Ig) serology of 446 newly-diagnosed multiple myeloma (MM) patients of the GMMG-MM5 phase III trial with a median follow-up of 58 months.

**Results:** CMV IgG and IgM positivity was seen in 51% and 6% of the patients, respectively. In multivariate analysis CMV IgG and CMV IgM serology show an age-depending effect for PFS. We identified positive CMV IgG/positive CMV IgM serology as an age-depending beneficial factor on PFS.

**Discussion:** Younger patients with a positive CMV IgG/positive CMV IgM serology experienced a favorable effect on PFS, whereas a positive CMV IgG/positive CMV IgM serology at older age has a disadvantageous effect on PFS.

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CMV; CMV IgM; multiple myeloma; GMMG-MM5 Phase III Trial; autologous stem cell transplantation; maintenance therapy; CMV-Infection; age-depending effect

## Introduction

Cytomegalovirus (CMV) is a ubiquitous opportunistic pathogen, which can cause severe life-threatening infections in immunocompromised hosts, whereas symptomatic infection of healthy persons is rare [1–3]. The seroprevalence of antibodies against CMV in recipients and donors of hematopoietic stem cells is an established poor prognostic factor for patients receiving an allogenic stem cell transplantation with an increased non-relapse-related mortality [4, 5]. In patients with multiple myeloma (MM), the recently increasing use of novel immunotherapies, high-intensity chemotherapy and CAR-T-cell therapy induce pronounced immunosuppression, which may lead to apparent clinical CMV infections [6]. However, survival data from prospective trials analyzing the role of CMV serology in newly diagnosed patients with multiple myeloma is missing. Here, we investigated the influence of CMV status on outcome in patients of the prospective GMMG-MM5 phase III trial assigned to two different induction chemotherapy regimens, followed by high-dose melphalan with autologous stem cell transplantation (ASCT) and a consolidation/maintenance therapy for 2 years or until complete response (CR) [7–9]. The induction chemotherapy consisted of either three cycles VCD (bortezomib, cyclophosphamide, dexamethasone) or PAd (bortezomib, doxorubicin, dexamethasone). Determining the CMV

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immunoglobulin (Ig) serologies of 446 patients we found no significant differences in treatment adherence and progression-free (PFS) and overall survival (OS) between IgG-positive or -negative specific CMV serology. However, a CMV specific IgG/IgM serology showed an age-depending effect on PFS.

## Patients and methods

### Study design

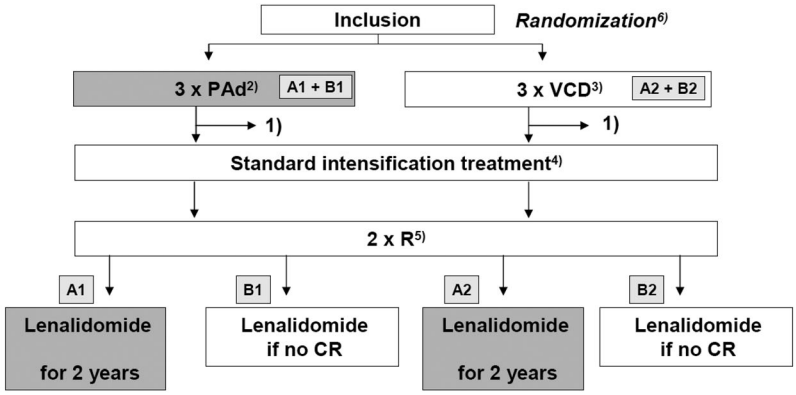
After written informed consent was given, the prospective, multicenter phase III GMMG-MM5 trial (EudraCT No. 2010-019173-16) enrolled transplant-eligible patients from 18 to 70 years of age with previously untreated, newly diagnosed MM (Figure 1). Two primary endpoints were investigated and reported previously [7–9]. The trial met its first primary endpoint and showed non-inferiority of three cycles VCD (bortezomib, cyclophosphamide, dexamethasone) compared to PAd (bortezomib, doxorubicin, dexamethasone) with regard to the rates of very good partial remission (VGPR) or better after induction therapy. The analysis of the second primary endpoint (PFS) showed no significant difference between the four treatment arms, combining the two induction therapies with two different maintenance strategies (lenalidomide (15 mg/d) for 2 years or until CR; Figure 1). The trial was approved by ethics committees of all participating sites and was conducted according to the European Clinical Trial Directive (2005) and the Declaration of Helsinki.

### Design of the current analysis

Overall, 604 patients were enrolled into the GMMG-MM5 trial. CMV IgG and IgM serology of 446 patients of 601 patients were available and analyzed. Database lock for the trial was June 2017.

### Statistical design and analysis

Two-group comparisons of distributions of baseline characteristics were assessed by Fisher's exact test for categorical variables and by the Mann–Whitney test for continuous variables. Time from randomization to disease progression or death from any cause defined PFS. Time from randomization to death from any cause defined OS. The Kaplan–Meier method was used to estimate survival distributions. Median follow-up times were calculated based on the reverse Kaplan–Meier method [10]. Survival curve comparisons between CMV IgG and IgM serologies were investigated using log-rank tests. For further evaluation of the effect of CMV serology on OS and PFS, multivariable Cox regression models were applied adjusting for age, sex, treatment arm and the International Staging System (ISS). In addition, we evaluated interactions between




1) Risk assessment within first 4 weeks of therapy; high risk patients may go off protocol with participation in an experimental phase II trial (e.g., allogeneic transplantation)
2) PAd = Bortezomib, Adriamycin, Dexamethasone
3) VCD = Bortezomib, Cyclophosphamide, Dexamethasone
4) Standard intensification treatment according to local protocol
5) R = Lenalidomide
6) Randomisation to one of four treatment strategies using block randomisation stratified by ISS stage

**Figure 1.** Flow chart and study population of the GMMG-MM5 trial. Overall, 604 transplant-eligible patients with newly-diagnosed MM between the ages of 18 and 70 were randomized into four different treatment arms (A1, A2, B1 and B2). Induction treatment consisted either of three cycles PAd (A1 and B1) or VCD (A2 and B2). Maintenance therapy was applied for 2 years (A1 and A2) or until CR (B1 and B2). All patients received high-dose melphalan (200 mg/m$^2$) followed by autologous stem cell transplantation and two cycles of a lenalidomide consolidation therapy. Patients not achieving a near CR or CR were offered a second transplant. The current analysis was performed on the safety population, consisting of patients who received at least one dose of trial medication (6 patients excluded who did not received allocated medication). Furthermore, 14 patients were excluded since route of administration changed during ongoing induction.

CMV status and age and sex, respectively. Results were described by hazard ratios (HR) and corresponding 95% confidence intervals (95% CI). All analyses took into account that CMV measurements were taken at different time points ('delayed entry'). All reported *p*-values were two-sided and considered to be statistically significant if they were smaller than 0.05. Statistical analyses were performed using R version 4.2.1 [11].

## Results

### *Prevalence of CMV serology positivity*

We analyzed 446 newly diagnosed MM patients who were enrolled within the prospective, multicenter phase III GMMG-MM5 trial (EudraCT No. 2010-019173-16). Serum samples were available for 169 (37.9%) patients at baseline, 234 (52.5%) patients at mobilization and 43 (9.6%) patients after ASCT. CMV IgG positivity was seen in 227/446 (50.9%) patients and 28/446 (6.3%) patients were positive for CMV IgM. While the proportion of IgG positive patients was similar at the three time points, IgM positivity slightly increased from baseline (7/169, 4.1%), to mobilization (16/234, 6.8%) and to ASCT (5/43 patients, 11.6%).

There were no significant differences in baseline clinical characteristics between patients with positive or negative CMV IgG serology (Table 1). CMV IgM-positive serology was more prevalent in VCD arms A2 and B2 ($n = 21/302$; 6.9%) compared to PAd arms A1 and B1 ($n = 7/299$; 2,3%; $p = 0.01$). The proportions of patients completing induction therapy, receiving a first and second ASCT, beginning lenalidomide consolidation and maintenance were similar among patients with a positive or negative CMV IgG status. Regular study completion and median time to premature withdrawal within the study from any cause were not different between both groups. Further, the frequency and grading of adverse events (AE) and serious adverse events (SAE) according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0.) for patients with a positive CMV IgG status were not statistically different compared with patients with CMV IgG negative serology.

**Table 1.** Comparison of CMV IgG and IgM prevalence between randomization arms.

| Variable | Effect | Hazard ratio | 95% confidence limits | |
|---|---|---|---|---|
| Treatment | A1:B2 | 0.88 | 0.62 | 1.23 |
| | A2:B2 | 0.90 | 0.65 | 1.25 |
| | B1:B2 | 0.83 | 0.59 | 1.18 |
| Gender | Female:Male | 0.82 | 0.64 | 1.05 |
| ISS | II:I | 1.28 | 0.95 | 1.73 |
| | III:I | 1.87 | 1.39 | 2.52 |
| Age (years) | 10 years* | | | |
| CMV IgG/IgM | | | | |
| neg/neg | | 0.92 | 0.75 | 1.14 |
| pos/neg | | 1.10 | 0.87 | 1.38 |
| pos/pos | | 3.05 | 1.33 | 6.97 |
| CMV IgG/IgM | pos/neg:neg/neg | | | |
| Age 55 | | 0.95 | 0.72 | 1.25 |
| Age 65 | | 1.13 | 0.82 | 1.56 |
| CMV IgG/IgM | pos/pos:neg/neg | | | |
| Age 55 | | 0.59 | 0.29 | 1.23 |
| Age 65 | | 1.96 | 1.04 | 3.70 |

*Hazard ratios and confidence intervals are computed for a 10 years change in age, dependent on CMV serology, and for CMV serology at the age of 55 and 65 years.

### *Impact of CMV serology on survival*

Median follow-up was 58 months and a total of 269 progression events occurred (IgG positive: 135; IgG negative: 134). The CMV IgG positive serology had no significant univariable effect on PFS compared to

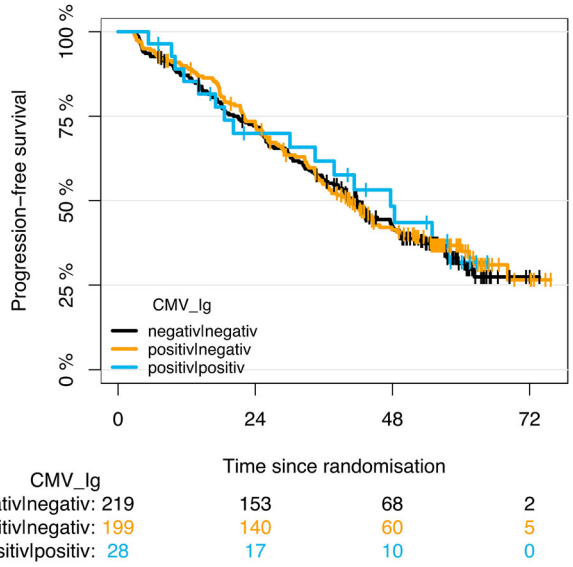



**Figure 2.** Progression-free survival in CMV IgG-negative/CMV IgM-negative patients, CMV IgG-positive/CMV IgM-negative patients and CMV IgG-positive/CMV IgM-positive patients. No statistically significant differences between the three PFS curves were found ($p = 0.93$).

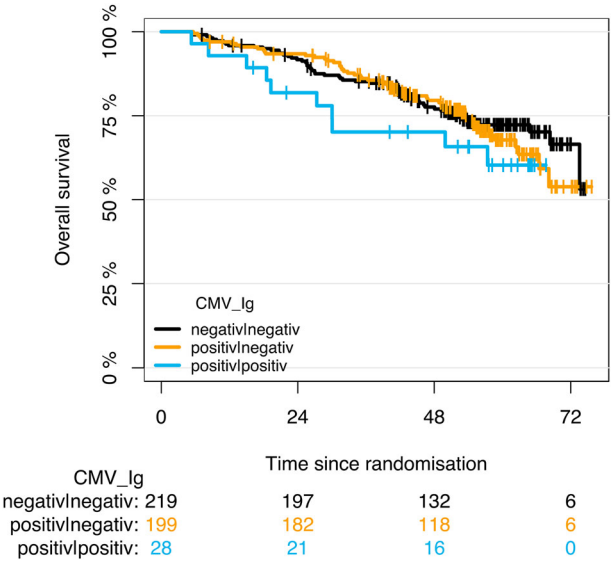



**Figure 3.** Overall survival in CMV IgG-negative/CMV IgM-negative patients, CMV IgG-positive/CMV IgM-negative patients and CMV IgG-positive/CMV IgM-positive patients. No statistically significant differences between the three OS curves were found ($p = 0.44$).

CMV IgG negative serology (Figure 2). PFS curves were also not statistically different between patients with positive CMV IgM serology and patients with negative CMV IgM serology (Figure 3). Overall, 122 deaths occurred during the observation period (IgG positive: 65; IgG negative: 57). No significant univariable effect of positive IgG serology on OS was observed. A positive CMV IgM serology was slightly associated with larger hazard of death compared to CMV IgM negative serology, but this was not statistically significant ($p = 0.21$).

Jacobsen et al. recently showed an age-dependent impact of CMV infections on outcome of AML patients after allogeneic transplantation, with younger CMV-positive patients having improved survival [12]. Therefore, we looked for interactions between CMV status and age and sex, respectively, in a multivariate model, which also included study arms (A1, A2, B1, B2) and ISS stage. Indeed, we identified a statistically significant CMV serology x age interaction effect on PFS ($p = 0.009$). This result is illustrated in Figure 4. For illustration, male patients <55 years had an advantageous effect with a HR of 0.4 compared to male patients <55 years with a negative CMV IgM serology, whereas older male patients at the age of 65 years with a positive CMV IgM serology had an increased risk for progress with a HR of 1.6 ($p = 0.005$) compared to male patients at the age of 65 years with a negative CMV IgM serology (Figure 4). Such an association was also seen between CMV IgG status and age, but not being statistically significant ($p = 0.08$). No statistically significant interaction effects of CMV IgG and IgM serology with patient's sex was observed.

## Discussion

This exploratory study revealed that approximately half of the study patients with untreated multiple myeloma (50.9%) had experienced a CMV infection in their lifetime and developed a positive CMV IgG

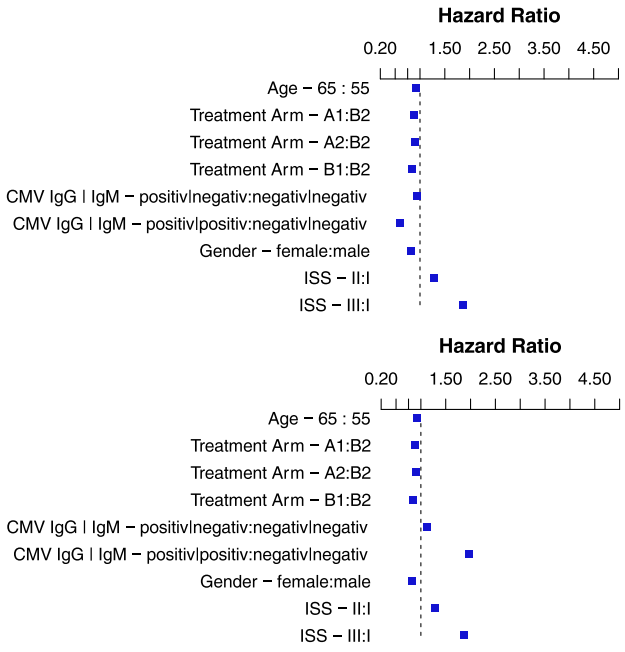



**Figure 4.** Age-CMV serology interaction. The interaction effect is illustrated by approximate curves in patients at age 55 and 65. Younger patients with a positive CMV IgG/positive CMV IgM serology at the age of 55 experienced a favorable effect on PFS with a HR of 0.59 compared to patients with a negative CMV IgG/negative CMV IgM status, whereas a positive CMV IgG/positive CMV IgM serology at the age of 65 has a disadvantageous effect on PFS with a HR of 1.96 compared to patients with a negative CMV IgG/negative CMV IgM serology.

serology. This is in concordance with the prevalence of a positive CMV IgG serology reported in healthy stem cell donors in Germany [13, 14]. Further, we found a considerable number of 6.3% of patients with a prevalence of a positive CMV IgM status in our study, which was higher than the reported prevalence of 1–4.6% in healthy women of reproductive age across Europe [15]. Notably, a positive CMV IgM serology was found at baseline in seven (4.1%) patients. At this time-point all patients were therapy-naïve, meaning that patients with multiple myeloma may have a slightly higher immunocompromised status at diagnosis with regard to CMV de-novo Infection. However, the proportion of a positive CMV IgM serology increased after mobilization and after stem cell transplantation to 6.8% and 11.6% of patients, respectively. Interestingly, all of the active CMV infection with a positive CMV IgM status had an inconspicuous clinical course. CMV IgM-positive serology was more prevalent in VCD arms A2 and B2 ($n = 21/302$; 6.9%) compared to PAd arms A1 and B1 ($n = 7/299$; 2,3%; $p = 0.01$). This may indicate that induction therapy with the combination of bortezomib, cyclophosphamide and dexamethasone induces more pronounced immunosuppression with regard to viral infections than the combination of bortezomib, doxorubicin and dexamethasone. The more pronounced immunosuppression of VCD detected here, might be caused not solely by cyclophosphamide alone, but in part by a higher total dose of dexamethasone (total dose of 320 mg per cyclus) compared to PAd (total dose of 240 mg per cyclus). Yet, no cases of severe CMV infection were recorded, demonstrating that the clinical course of CMV infection was mild in all cases. However, the serological CMV status is possible to change overtime during treatment, which was not evaluated here.

Surprisingly, we found an age-depending beneficial effect of a positive CMV IgG/positive CMV IgM serology on PFS. We found out, that younger patients with a positive CMV IgG/positive CMV IgM serology experienced a favorable effect on PFS compared to patients with a negative CMV IgG/negative CMV IgM status, whereas a positive CMV IgG/positive CMV IgM serology in older patients had a disadvantageous effect on PFS compared to those with a negative CMV IgG/negative CMV IgM serology. This supports the hypothesis that CMV serology has an impact on PFS. The observed effect on PFS did not translate into overall survival differences between CMV IgG- and IgM-positive or IgG- and IgM-negative patients. Yet, we appreciate that only 28 patients had a positive CMV IgM serology in our study.

An age-depending anti-leukemic effect of CMV infection in AML patients after allogeneic transplantation was first described 1990 by Jacobsen et al. from the Nordic Bone Marrow Transplantation Group. They found that young donor age and a posttransplant CMV infection of patients had a considerable graft-versus-leukemia activity in patients with chronic graft-versus-host disease [12]. Further, Elmaagacli et al. showed that a positive CMV IgG status as well as a documented CMV reactivation reduced the risk for leukemic relapse in patients transplanted for AML (median age 47 years) [13]. In another study, CMV reactivation was also associated with a reduced risk for relapse in patients transplanted for aggressive lymphoma (median age of 48 years) [16].

It is known that CMV seropositivity increases with age in all populations [17]. Chronic infection with CMV is associated with a deterioration of the immune system that affects adaptive and innate immunity. CMV infection contributes as one of the major drivers of age-depending immune dysfunction, defined as immunosenescence and entailing changes in abundance, phenotype, and function of NK cell subsets. Thus, the repertoire of NK cells is altered in CMV seropositive human individuals during ageing [17–20]. An example of it is an increase in the number of NKG2C-positive NK cells in elderly individuals, while the number of NK cells bearing cytotoxicity receptors NKp30 or NKp46 decreases [18, 19]. Therefore, it is possible that CMV-induced NK and T-cell population subsets mediate an anti-myeloma effect in younger MM patients, while this immunostimulatory effect gets weaker in elderly patients as a result of immunosenescence. However, the effects on PFS described here must be taken with caution due to low number of study-patients with an active CMV infection (i.e IgM seropositivity).

Detection of CMV DNA in the blood of multiple myeloma patients as an indicator for CMV reactivation was performed and reported by Tay et al. [21]. They found CMV DNA in the blood of 6 out of 62 patients with multiple myeloma. In their study, patients were tested for CMV DNA at different disease stages and combinations of therapies, as well as during treatment-free intervals. The rate of CMV IgM-positive prevalence of 6.3%, detected here by positive CMV IgM serology, was unexpectedly high and showed that CMV reactivation could be of clinical relevance in the treatment of MM. This might become more important in the future due to the increasing use of novel immunotherapies, including monoclonal and bispecific antibodies, high-intensity chemotherapy and CAR-T-cell therapy, all inducing more pronounced immunosuppression. MM treatment-associated immunosuppression might induce clinically apparent CMV infections.

Taken together, our exploratory analysis of the prospective GMMG-MM5 study represents the largest investigation of CMV infection with positive IgM serology from a prospective phase III trial. We demonstrate that a potential CMV infection is frequently detectable at time points of baseline, mobilization and after stem

cell transplantation. Notably, we found an unexpected age-depending beneficial effect of a positive CMV IgG/positive CMV IgM serology on PFS, which was never described before.

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## Disclosure statement

No potential conflict of interest was reported by the author(s).

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## Author contributions

Conception and design: HS, AE, NW, HG, EKM, DH, KM and AB. Responsible statisticians: AB and KM. Administrative support: HG, EM, and SPL. Provision of study materials or patients and/or collection, assembly and review of data: all authors. Data analysis and interpretation: HS, AE, NW, HG, EKM, KM and AB. Writing of the first manuscript draft: HS, AE, EKM, MMu, KW, DH, NW, MSR and HG. Manuscript editing, discussion of trial data/results, and final writing: all authors. Final approval of manuscript: all authors.

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