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Current management of CMV infection in cancer patients (solid tumors). Epidemiology and therapeutic strategies

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ABSTRACT

Little evidence is available regarding the incidence of CMV disease in patients with solid cancers. Latest data show that approximately 50 % of these patients with CMV PCR positivity developed clinically relevant CMV-viremia, and would require specific therapy. In the clinical arena, CMV reactivation is an important differential diagnosis in the infectological work up of these patients, but guidelines of management on this subject are not yet available. CMV reactivation should be considered during differential diagnosis for patients with a severe decline in lymphocyte counts when receiving chemoradiotherapy or immunochemotherapy with lymphocyte-depleting or blocking agents. Monitoring of CMV reactivation followed by the implementation of preemptive strategies or the establishment of early antiviral treatment improves the prognosis and reduces the morbidity and mortality of these patients.

Keywords: Cytomegalovirus, cancer patients, lymphopenia, antiviral preemptive strategy

INTRODUCTION

Cytomegalovirus (CMV) is an important cause of both morbidity and mortality in solid organ or stem-cell transplanted patients and immunocompromised hosts, including cancer patients [1-3]. CMV reactivation especially in immunocompromised patients may rapidly progress to a fatal CMV disease. Patients with CMV infection have a wide variety of clinical manifestations, including fever, enterocolitis, pneumonitis, retinitis, hepatitis, encephalitis, nephritis, and disseminated disease [4]. The exact mechanism of the reactivation of CMV is not well established; however, the disturbance of the host's immune defences plays an important role [5]. Immune impairment in patients with malignancies was considered to be a risk factor for CMV disease. The term "CMV infection" indicates latent and asymptomatic form of infection, whereas the "CMV disease" means symptomatic end-organ involvement [6].

The relevance of infection and reactivation in haematological patients has been a matter of interest, although efforts have fundamentally focused on reactivation in the post-allogenic haematopoietic stem cell transplant (HSCT) patient cohort. Newer transplant modalities have been progressively introduced in the clinical setting, with successively more drugs being used to manipulate graft composition and functionality. Less is known about the effects of CMV in terms of mortality or disease progression in patients with other malignant haematological diseases or solid neoplasms who are treated with immunochemotherapy or new molecules, or in patients who receive autologous SCT. The absence of serious consequences in these groups has probably limited the motivation to deepen our knowledge of this aspect.

However, the introduction of new therapeutic agents for solid and haematological malignancies has led to a better understanding of how natural killer (NK) cells, CD4+ and CD8+ T lymphocytes, and B lymphocytes interact, and of the role of CMV infection in the context of recently introduced drugs such as modern immunochemotherapies, immune check-point inhibitors such as programmed cell death-1 (PD-1) or programmed cell death-ligand 1 (PD-1L) inhibitors and cytotoxic T-lymphocyte antigen 4 (CTLA4) inhibitors, Bruton tyrosine kinase (BTK) inhibitors, phosphoinosytol-3-kinase (PI3K) inhibitors, Janus-kinase (JK) inhibitors, proteasome inhibitors, anti-CD52 blocking agents, purine analogues, anti-BCL2 drugs, and even CAR-T cells therapy [7].

Because of all this, the incidence of CMV infection in patients with malignancies varies widely in different studies [8,9]. However, only limited data is available on the role of CMV reactivation/disease in patients with solid cancers e.g. under

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chemotherapeutic treatment or direct anti-target immunotherapies. In the clinical experience of various centers, CMV reactivation is an important differential diagnosis in the infectological workup of these patients, but guidelines of management on this subject are not available yet.

CYTOMEGALOVIRUS INFECTION AND ITS CLINICAL IMPACT IN PATIENTS WITH SOLID TUMOURS

To date, only a few small case reports, some observational studies or post-mortem analyses are available. A single centre study that analysed 107 patients with CMV disease during 2008-2009, including 75 with solid cancer, reported a mortality rate of 61.3 % in the solid organ malignancy group [10]. With an overall mortality rate of 56.1% (60/107), worse outcomes were observed in patients with solid organ malignancies than in those with haematological malignancies (mortality rate of the haematological malignancy group: 43.8%). Mechanical ventilation, leukocytosis, and lack of appropriate early treatment were independent predisposing factors of mortality. Furthermore, CMV viremia was associated to higher mortality rates in cancer patients. In a retrospective post-mortem analysis of 47 cancer patients with histologically proven gastrointestinal CMV disease, 13 patients had an underlying solid cancer [11]. An older report demonstrated a CMV attributable mortality of 42% in a study cohort including both haematological and solid tumour malignancies [12], although the objective of this study was to estimate the frequency of CMV pneumonia and describe its clinical and radiological presentation in adult non-transplantation patients with cancer. Of the 10,441 autopsies performed during the period of January 1964 through December 1990, 9,029 were evaluable. Twenty histopathologically confirmed cases of CMV pneumonia were found, representing a frequency of 2.2 cases per 1.000 autopsies. When the frequency of CMV pneumonia was compared for the periods 1964-1979 (1.5 cases per 1.000 autopsies) and 1980-1990 (4.6 cases per 1,000 autopsies), it was significantly increased directly related to the number of patients with solid malignancies ($p < .05$). At that time (mid-1990s), the authors from the M.D. Anderson Cancer Center (Houston) concluded that CMV pneumonia was an uncommon diagnosis at autopsy for adult non-transplantation patients with cancer, and that was usually found in conjunction with a disseminated neoplastic process.

These data could suggest that a reliable risk of CMV reactivation/disease exists in solid cancer patients. In a more recent definitive study, the incidence and impact of CMV reactivation in solid cancer patients was investigated by performing a retrospective analysis of a single centre CMV database [13]. The authors retrospectively examined the occurrence of CMV reactivation in patients with solid tumours, resulting in 107 solid cancer patients testing positive for CMV reactivation, out of 890 CMV-positive blood serum samples of mainly haematological and oncological patients. Seventeen patients with solid cancer and a positive CMV-PCR test were identified, of which eight patients had clinically relevant CMV disease and received prompt antiviral treatment. While five patients fully recovered, but despite prompt antiviral treatment three patients died. Of them, two had significant co-infections with another pathogen (Epstein Bar Virus and *Aspergillus*, respectively), which could indicate that CMV reactivation was at least one factor contributing to sepsis. Patients with poor outcomes had progressive underlying neoplastic disease and were receiving adjuvant or salvage chemotherapy. The authors concluded that CMV reactivation and disease might be underestimated in routine clinical practice. In their retrospective analysis they showed that approximately 50% of patients suffering from solid cancers with a positive CMV polymerase chain reaction also had clinically relevant CMV disease requiring antiviral therapy.

The summarized studies show the clinical impact of CMV reactivation and viremia in solid tumour patients. Accumulating data suggest that CMV disease in these patients is more frequent than previously estimated. Furthermore, it must be pointed out that CMV testing is not routinely done in clinical practice and that therefore CMV reactivation or disease may be underreported. Due to the lack of consensus and specific guidelines on CMV infection in patients with solid neoplasms, the positivity cut-off points and significance of CMV viral load (VL) in these patients may vary and differ between different centres and publications. Significant CMV VL was considered to be above >1,000 copies/ml in some studies. However, more recent evidence places the potentially significant viremia above 4,000 copies/ml [13]. Since approximately 50% of patients with CMV PCR positivity would develop clinically relevant CMV-viremia, they would require specific anti-CMV therapy. The early administration of specific antiviral treatment may improve the outcome of these patients and may avoid unsuccessful antibiotic therapy and prolonged hospitalization. Clinicians should be aware of the broad range of potential complications of CMV infection in these patients with solid tumours.

For all these reasons, it would be appropriate to propose the inclusion of routine CMV screening in solid cancer patients presenting with subacute or intermediate duration fever of unknown origin. Larger studies are necessary to identify risk factors for developing CMV disease in this subpopulation. Moreover, the raising number of elderly patients receiving chemotherapy for solid tumours and the fact that CMV incidence increases with age suggests that CMV reactivation and CMV disease are expected to increase in the near future.

A series of unanswered questions and unmet needs in the field of CMV infection in patients with solid tumours deserve to be addressed in the coming years (Table 1).

"UNEXPECTED" CMV INFECTION OR REACTIVATION IN RARE SOLID NEOPLASMS

Beyond merely anecdotal descriptions, series of experiences of CMV reactivation or infection have been reported in patients with very peculiar solid tumours. These special forms have been found mainly in patients with oesophageal cancer

Table 1 CMV infection/disease in solid cancer. Not covered issues

UNMET NEEDS	PENDING QUESTIONS
Scarce information and little evidence of studies or trials; Underestimation of cases	Does it reflect a greater net state of immunosuppression?
Therapeutic guidelines adapted to new non-transplanted immunocompromised hosts (oncohaematological patients, solid tumours)	Is CMV a marker or a consequence of active, uncontrolled neoplasm?
Reduce morbidity and mortality with earlier diagnosis and management	Routine CMV screening against prolonged fevers or unknown origin fever?
Education and training in high clinical suspicion of CMV in groups of emerging patients at risk	Which are the Risk Factors that promote CMV in these patients?
Need to establish consensus cut-off points for CMV viral load in these patients	Solid cancer, age and serostatus of CMV; higher prevalence with aging?
Reduce use of other antimicrobials and antifungals, and specifically treat only viral infection	
Avoid prolonged and unnecessary hospitalizations	

[14], malignant pulmonary mesothelioma [15], and aggressive brain neoplasms undergoing immunochemoradiotherapy protocols that include temozolomide [16,17]. Obviously without forgetting the possible influence of the quintessential anti-CD20 agent, rituximab, in the treatment of multiple oncohaematological neoplasms as a factor that promotes infection or reactivation by CMV [18].

In a retrospective study whose objective was to identify factors associated with CMV reactivation in patients with oesophageal cancer who were receiving chemoradiotherapy, CMV reactivation was not uncommon and was associated with the minimum lymphocyte counts [14]. This study included oesophageal cancer patients receiving definitive or palliative chemoradiotherapy; patients with fever during chemoradiotherapy underwent a systemic work-up to detect the primary focus of infection, and CMV antigenemia (period 2013-2020) was assessed in cases of unidentifiable infection. Among 132 patients, 124 received 5-fluorouracil plus cisplatin and 8 received oxaliplatin–5- fluorouracil–levofolinate chemotherapy. Overall, 19 patients had CMV reactivation, 37 had other infections, and 76 had no identified infection (groups 1, 2, and 3, respectively). Median minimum lymphocyte counts were 81.0/µl (interquartile range: 52.0–144.0/µl) in CMV reactivation group (1), with counts that were significantly lower than in other groups (2 and 3). This retrospective study demonstrated that lymphopenia caused by chemoradiation was associated with CMV reactivation, and that planning target volume had a greater effect on lymphopenia than the chemotherapy itself.

In a consecutive case series of 144 malignant pleural mesothelioma (MPM) patients, one group evaluated two biomarkers of CMV: IgG serostatus (defined as positive and negative) and DNAemia (>100 copies/mL of cell free CMV DNA in serum). Approximately half of the MPM patient population was CMV IgG seropositive (51%). CMV DNAemia was highly prevalent (79%) in MPM and independent of IgG serostatus [15]. DNAemia levels consistent with high level current infection (>1,000 copies/mL serum) were present in 41% of patients. Neither IgG serostatus nor DNAemia were associated with patient survival. In tissues, the authors observed that CMV DNA was present in 48% of tumours and only 29% of normal pleural tissue obtained from individuals without malignancy. These results suggested that nearly half of MPM patients have a high level current CMV infection at the time of treatment and that pleural tissue may be a reservoir for latent CMV infection.

Temozolomide is an alkylating agent, from the triazene family, which is administered orally. It has been used in tumours of the central nervous system (CNS), such as glioblastoma multiforme, refractory anaplastic astrocytoma, and others: brain metastases, refractory primary brain lymphoma, melanoma, etc. It is used in chemoradiotherapy schemes, and in associations with m-TOR inhibitors [16]. Among its adverse effects, it causes myelotoxicity, which leads to profound and prolonged lymphopenia, lasting 2-12 months, which for some groups is a reason to monitor CD4+ T lymphocytes, in order to make predictions about the increased risk of opportunistic infections [17].

In a prospective cohort of patients receiving this drug for neuroendocrine tumors in 2006, the overall incidence of opportunistic infections was 10 percent, while among patients receiving therapy for > or =7 months, the incidence was 20 percent [19]. Among the latter, CMV infections (13% in some series) and severe forms of the disease such as colitis, pneumonitis, and myelitis have been described. Few cases of TMZ-induced cytomegalovirus reactivation have so far been reported, and there are no guidelines regarding the use of chemotherapy after recovery from CMV reactivation. For this reason, many centres recommend monitoring CMV by periodic determination of antigenemia or DNAemia using molecular techniques [20].

In patients undergoing treatment with temozolomide, close surveillance of opportunistic infections (pneumocystosis, varicella-zoster, cytomegalovirosis, candidiasis) should be assessed, in addition to implementing narrow microbiological risk monitoring and pre-emptive treatment or antimicrobial prophylaxis strategies.

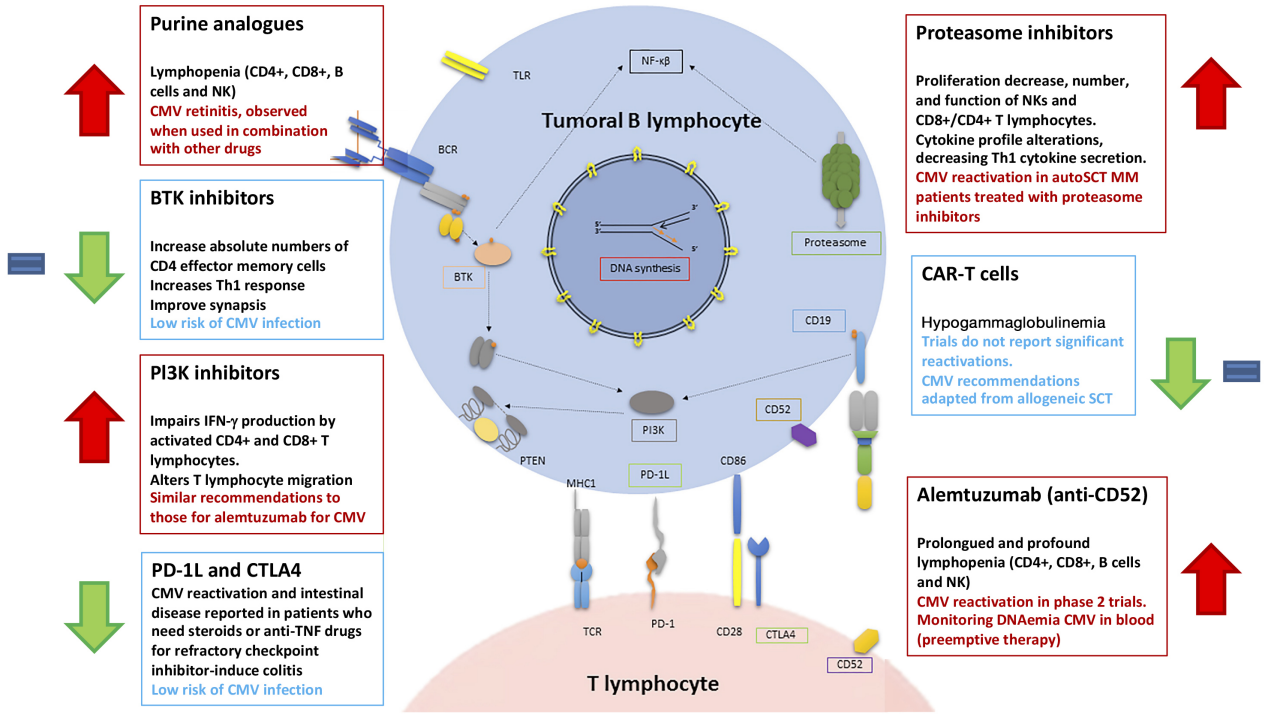

Figure 1 | **CMV infection/reactivation risk in the context of antitumoral drugs used in oncohaematological patients**

Red arrow: symbolizes increased risk of CMV reactivation or infection

Green arrow and equals sign: represent a decreased risk of CMV reactivation or infection or a situation similar to the group of patients related to the diagnosis who do not receive these drugs

BCR, B cell receptor; BTK, Bruton tyrosine kinase; CART cells, chimeric antigen receptor T cell; CMV, cytomegalovirus; CTLA4, cytotoxic T-lymphocyte antigen 4; MHC, major histocompatibility complex; NK, natural killer; PI3K, phosphatidyl inositol 3 kinase; PD, programmed death; PD-1L, programmed death-ligand 1; PTEN, phosphatase and tensin homologue; SCT, stem cell transplantation; TLR, toll-like receptor; MM, multiple myeloma.

Modified and adapted of reference 7 [Alonso-Alvarez S, et al. (2021) Cytomegalovirus in Haematological Tumours. Front. Immunol. 12:703256. doi: 10.3389/fimmu.2021.703256]

CMV IN OTHER ONCOHAEMATOLOGICAL SETTINGS: NEW DRUGS AND NEW THERAPIES IN LYMPHOPROLIFERATIVE SYNDROMES AND MULTIPLE MYELOMA

The introduction of new therapeutic agents for solid and haematological malignancies has led to a better understanding of how immune cells (NK cells, CD4+ and CD8+ T and B lymphocytes) interact, and of the role of CMV infection in the context of recently introduced drugs such as modern immunochemotherapies.

For reasons of extension of this manuscript, this section will be summarized in Figure 1 with additional comments. The figure shows how certain families of drugs or therapeutic strategies favour and increase the risk of CMV reactivation or infection in certain settings of oncohematological disease, and how others do not increase this risk or their influence is less or even neutral [7].

Without forgetting the weight and influence of corticosteroids (their dose and duration), the risk of CMV reactivation or infection is increased in the following groups of oncohaematological patients receiving new treatment modalities, such as: patients with lymphoproliferative syndromes treated with purine analogues, alemtuzumab (anti-CD52 agent) or PI3K inhibitors (idelalisib, e.g.), and patients diagnosed with multiple myeloma undergoing auto-HSCT and previously treated with proteasome inhibitors.

The risk of CMV infection and disease is not increased, and is even comparatively lower, in patients treated with Bruton's tyrosine kinase inhibitors, or with anti-PD-1L or CTLA4 agents, or in those receiving CAR- T [21]. There are documented cases of CMV reactivation in the first month and during the first three months after CAR-T cells therapy. Previous therapies, disease stage, and patient basal characteristics seem to be crucial. Regarding prophylaxis against viral infections, there are no unique international recommendations, and existing ones are heterogeneous. The European recommendations are based

on data from allogeneic transplant recipients. In general, antiviral prophylaxis is established with acyclovir or valacyclovir at least up to one year after CAR-T infusion, or until a CD4+ T lymphocyte count greater than 0.2 x 10^9/L is documented.

CONCLUSIONS

The relationships between CMV infection and oncohaematological pathologies is becoming better known, fundamentally, as a result of the important repercussions from the management of the infection and reactivation of the CMV in the post-transplant patients (post-allogeneic haematopoietic stem cells, or post-solid organ) [22]. The role of CMV in cancer has primarily focused on the presence of virus in tumours [23]. Less well described is the epidemiology of active CMV infection in solid tumour cancer patients. Although rare, CMV infection can be lethal in patients with cancer. However, the criteria for the prevention of CMV reactivation during solid cancer treatment are unclear. CMV reactivation should be considered in the differential diagnosis of patients with a severe decline in lymphocyte counts when receiving chemoradiotherapy or immunochemotherapy with lymphocyte-depleting or blocking agents. Furthermore, there are many other situations that give rise to severe immunosuppression, either due to the oncohaematological pathology itself or to the treatments used, which should prompt a close surveillance concerning the complications derived from infection by this virus. Thus, it is necessary to study the effect of new drugs on the immune system and so adapt CMV prophylaxis and infection monitoring to different treatment schemes and situations, now that new anti-CMV drugs with fewer secondary effects are available for this purpose. Whether CMV, either at the tumour site or as an active infection with positive DNAemia, is present in some solid tumours and contributing to patient outcomes is yet an insufficiently explored area of research [24].

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