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Cytomegalovirus DNAemia and disease: current-era epidemiology, clinical characteristics and outcomes in cancer patients other than allogeneic hematopoietic transplantation

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Cytomegalovirus DNAemia and disease: current-era epidemiology, clinical characteristics, and outcomes in cancer patients other than allogeneic haematopoietic transplantation

Abstract

Background and objectives

High-intensity chemotherapy and advances in novel immunotherapies have seen the emergence of cytomegalovirus (CMV) infections in cancer patients other than allogeneic haematopoietic cell transplantation (HCT). We therefore aimed to evaluate the epidemiology, clinical characteristics, and outcomes of CMV infection in this population.

Method

A retrospective review of cancer patients other than allogeneic HCT who had CMV DNAemia and/or disease from July 2013 till May 2020 at a quaternary cancer center was performed.

Results

Of 11,485 cancer patients who underwent treatment during this period, 953 patients had CMV DNA testing performed and 238 of them had CMV DNAemia. After excluding patients with allogeneic HCT, 62 patients with CMV DNAemia were identified of which 10 had concurrent CMV disease. The most frequent underlying malignancies were B-cell lymphoproliferative disease (LPD) (31%, 19/62), T-cell LPD (21%, 13/62), chronic lymphocytic leukemia (11%, 7/62), and multiple myeloma (10%, 6/62). Most patients had lymphopenia (77%, 48/62), multiple cancer therapies (63%, 39/62 received ≥2 previous therapies), co-infection (56%, 35/62 had ≥1 co-infection) and corticosteroid therapy (48%, 30/62) within one month before CMV diagnosis. CMV DNAemia and disease were observed in patients receiving novel immunotherapies including bispecific antibody therapy, chimeric-antigen receptor T-cell therapy and immune checkpoint inhibitors.

Conclusion

Patients with haematological malignancy, particularly B-cell LPD, T-cell LPD, chronic lymphocytic leukemia and multiple myeloma were frequently identified to have CMV DNAemia and disease. Lymphopenia, multiple cancer therapies, co-infection, and recent receipt of systemic corticosteroids were also commonly observed. Future studies are necessary to determine optimal identification and management of CMV in these patients.

Cytomegalovirus DNAemia and disease: current-era epidemiology, clinical characteristics and outcomes in cancer patients other than allogeneic hematopoietic transplantation

Introduction

Cytomegalovirus (CMV) has a worldwide distribution and infects up to 90% of adults, leading to lifelong latent infection.(1) Reactivation of latent CMV infection is usually detected via monitoring as CMV DNAemia, but may result in progression to severe end-organ disease causing substantial morbidity and mortality in solid organ or allogeneic hematopoietic cell transplant (HCT) recipients. Outside of the transplant setting, high-intensity chemotherapy with the introduction of novel immunotherapeutic agents over the past decade has highlighted that CMV DNAemia and end-organ disease may be of clinical importance in other cancer populations. Administered to heavily pre-treated patients and coupled with other chemotherapeutic agents, these therapies may increase the risk of CMV-related complications. Historically, risks for CMV DNAemia and disease in settings other than allogeneic HCT have been considered low.

The objectives of this study were: (i) to determine the epidemiology of CMV DNAemia and end-organ disease in current-era patients with solid tumours and non-allogeneic HCT hematological malignancy and (ii) to describe clinical characteristics, natural history and treatment outcomes of CMV in these populations.

Methods

Design and inclusion/exclusion criteria

A retrospective review of patients with haematological and solid organ cancers undergoing treatment at Peter MacCallum Cancer Centre between 1st July 2013 and 31st May 2020 was performed. All patients with a positive CMV polymerase chain reaction (PCR) from blood or CMV inclusions on tissue histopathology were included. Allogeneic HCT recipients and patients with CMV detected by PCR on urine, mucosal and/or skin swab samples only were excluded. This study was approved by the institutional review board.

Identification of cases and data collection

Laboratory and histopathology databases were searched to identify all patients with a positive CMV PCR from blood or CMV end-organ disease. Pharmacy records identified patients who had been treated with anti-CMV therapy.

Clinical and electronic medical records were reviewed to identify clinical characteristics at the time of CMV DNAemia and/or disease, CMV serological status, and other features such as lymphopenia, number of previous lines of therapy, type of co-infection, and corticosteroid therapy within 1 month prior to CMV diagnosis. Medical charts were reviewed for at least 6 months from the time of CMV diagnosis.

Cancer-related therapy within one month of CMV diagnosis was classified as conventional chemotherapy, fludarabine-containing therapy, monoclonal antibody therapy, bispecific antibody therapy, antibody-drug conjugates, targeted therapy, immune checkpoint inhibitors, and cellular therapies like chimeric-antigen receptor T-cell (CAR T-cell) and autologous transplantation. CAR T-cell therapy patients who received fludarabine and cyclophosphamide conditioning were included only into CAR T-cell therapy group. The cumulative incidence of CMV for each therapy was determined by evaluating the number of patients diagnosed with CMV DNAemia and/or disease within each subgroup divided by the total number of patients treated with each regime during the study period.

Definitions

CMV DNaemia was defined as the isolation of CMV in plasma by a PCR-based technique. CMV disease was defined as clinical symptoms and/or radiological evidence consistent with CMV end-organ infection together with histopathological or immunohistochemical features of CMV on tissue biopsy specimens. (2) A line of therapy consisted of ≥1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens. A treatment was considered new line of therapy if a treatment regimen was discontinued for any reason and a different regimen was started. In patients undergoing > 1 autologous HCT, each HCT was also considered a new line of therapy. Co-infection was defined as any documented infection within 1-month pre- and post-CMV diagnosis. Invasive fungal disease was defined based on consensus definitions from the EORTC/MSGERC 2019 criteria. (3) Corticosteroid therapy was defined as administration of ≥0.5mg/kg/day of prednisolone, or equivalent potency for at least 2 weeks within 1 month prior to CMV diagnosis while high dose corticosteroids referred to

≥1mg/kg/day of prednisolone, or equivalent potency for at least 2 weeks. (4) Lymphopenia was defined as total absolute lymphocyte count of $< 1 \times 10^9$/L at the time of CMV diagnosis.

Cytomegalovirus testing

At our institution, CMV PCR testing was not routinely performed but tested at the discretion of the treating physicians, as clinically indicated. However, in patients receiving alemtuzumab, weekly monitoring of CMV PCR was routinely performed during and post therapy. Patients receiving idelalisib were also screened for CMV DNAemia following recommendations by regulatory authorities in 2018. (5)

Quantitative CMV viral load (VL) was performed on plasma specimens using the Abbott RealTime CMV PCR assay. All patients with positive qualitative CMV PCR from blood specimens have quantification of CMV VL.

Local management of CMV DNAemia and/or disease

CMV therapies that were used during this study period include intravenous ganciclovir 5mg/kg every 12 hours and oral valganciclovir 900mg every 12 hours (adjusted for renal function). Intravenous foscarnet 90mg/kg every 12 hours was used for patients who experienced haematological toxicity during ganciclovir or valganciclovir therapy. For patients with haematological malignancy, institutional policy for transfusion of blood products was consistent during the study period whereby CMV negative recipients received blood products from donors that were serologically negative for CMV.

Statistical analysis

All data were analysed using IBM Statistical Package for Social Sciences (SPSS) statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). Data were expressed as mean and

standard deviation for normally distributed continuous variables, median and range for non-normally distributed continuous variables, and number/proportion for categorical variables.

Results

A total of 11,485 cancer patients underwent cancer-related treatment during the study period, including 2,705 patients with hematological malignancy and 8,780 patients with solid organ malignancy. Of 953 patients who had CMV PCR testing performed, 238 (25%, 238/953) were found to have positive CMV PCR from blood specimens. After excluding patients who developed CMV DNAemia and/or disease only after allogeneic HCT, 62 (26%, 62/238) patients fulfilled inclusion criteria, with 10 (16%, 10/62) having CMV disease. (Figure 1)

Clinical characteristics at the time of CMV diagnosis

Among the 62 patients who had CMV DNAemia and/or disease, the median age was 67 years (range, 35-87 years) and 40 (65%, 40/62) were male. Fifty (81%, 50/62) had underlying haematological malignancy while 12 (19%, 12/62) had solid organ malignancy. The most frequent underlying malignancy was B-cell lymphoproliferative disease (LPD) (31%, 19/62), T-cell LPD (21%, 13/62), chronic lymphocytic leukemia (11%, 7/62), and multiple myeloma (10%, 6/62). Of the patients with underlying T-cell LPD, 11 (85%, 11/13) had cutaneous T-cell lymphoma receiving alemtuzumab therapy. When analysed by underlying cancer diagnosis, the cumulative incidence of patients with CMV DNAemia and/or disease ranged between 0.1-2.2%, with hematological malignancies having higher rates than solid organ malignancies (Table 1).

Patients had a median of two lines of therapy (range, 0-8) prior to CMV diagnosis and 39/62 (63%) had received two or more therapies. Median duration before diagnosis of CMV DNAemia the lines of therapy were considered were 32 days (range, 7-210 days). Forty-eight

patients (77%, 48/62) had lymphopenia at the time of CMV diagnosis. Thirty patients (48%, 30/62) were administered corticosteroid therapy within one month prior to CMV diagnosis of which 11 (37%, 11/30) received high-dose corticosteroids. The main indication for high-dose corticosteroids were autoimmune-related adverse reactions (7/11), hemophagocytic lymphohistiocytosis (2/11), and cytokine release syndrome (2/11). Of note, 4 (36%, 4/11) patients developed CMV end-organ disease.

Fifty-seven patients (92%, 57/62) had baseline CMV serology and all were CMV IgG positive. Forty-six patients (74%, 46/62) received anti-herpes simplex virus prophylaxis (oral valacyclovir 500mg once daily) at the time of CMV diagnosis.

Cancer-related therapy at the time of CMV diagnosis

CMV DNAemia and/or disease was detected in patients receiving conventional chemotherapy, fludarabine-containing chemotherapy, autologous transplantation, idelalisib, bispecific T-cell engager (BiTE) antibody therapy, CAR T-cell therapy, brentuximab vedotin, and monoclonal antibody therapy such as rituximab, obinutuzumab, and alemtuzumab. (Table 2) CMV diagnosis was not found in haematological patients receiving other novel therapies such as Bruton tyrosine kinase inhibitors or B-cell lymphoma 2 inhibitors.

Alemtuzumab therapy was associated with an overall 48% cumulative incidence of CMV. This was higher than the cumulative incidence among patients taking idelalisib (15.4%), CAR T-cell therapy (6.5%), brentuximab vedotin (4%), BiTE therapy (3.8%), and fludarabine-containing therapy (2.9%). Other cancer treatment subgroups had less than 2% cumulative incidence of CMV diagnosis.

Co-infections

In total, 35/62 (56%) patients had at least one co-infection within one month of CMV diagnosis; 22/35 (63%) had one and 13/35 (37%) had at least two co-infections.

Nine patients had 11 episodes of invasive fungal disease (IFD). (Table 3) Four were diagnosed after CMV diagnosis (median number of days: 9, range, 4-21 days) while the remaining IFD cases were diagnosed before CMV DNAemia and/or disease (median number of days: 5, range, 4-26 days). These 9 patients were heavily pretreated, having a median of 3 previous therapies (range, 2-6), and all received steroid therapy. All patients (100%, 9/9) were lymphopenic at the time of IFD diagnosis and seven (78%, 7/9) died within 3 months of CMV diagnosis.

Characteristics of patients with CMV DNAemia only

Fifty-two patients (84%, 52/62) had CMV DNAemia but no evidence of end-organ disease. Persistent unexplained fever (33%, 17/52), chest imaging abnormalities (29%, 15/52), and gastrointestinal symptoms (25%, 13/52) were the most common clinical characteristics in these patients. Thirteen (13/52, 25%) symptomatic DNAemia patients underwent a diagnostic investigation (bronchoscopy or colonoscopy) for CMV disease which was negative. The remaining (39/52, 75%) of symptomatic DNAemia patients did not receive investigations for end-organ disease. Patients with CMV DNAemia that received anti-CMV therapy (23/52, 44%) were given valganciclovir (83%, 19/23) or ganciclovir (17%, 4/23) for a median of 22 days (range, 6-58 days). Prior steroid use was observed in 52% (12/23) and all treated patients underwent weekly CMV VL monitoring with 72% (18/23) achieving CMV negativity. Fourteen (61%, 14/23) were hospitalised for a median of 28 days (range, 4-35 days).-Those that received anti-CMV therapy were observed to have higher CMV VL as compared to those who were not treated (median CMV VL of 5,105 IU/ml (range, 99-11,362,095 IU/ml) vs 411 IU/ml (range, 33-2,127 IU/ml)). Of patients who did not receive anti-CMV therapy (56%, 29/52), nobody progressed to CMV disease.

Characteristics of patients with CMV disease

Ten patients were diagnosed with CMV disease, including 9 patients (90%, 9/10) with CMV gastrointestinal disease and 1 patient (10%, 1/10) with CMV retinitis. (Table 4) All patients with histopathologically proven CMV disease had concurrent CMV DNAemia. The median CMV VL at time of diagnosis was 5,806 IU/ml (range, 290- 1,122,388 IU/ml). Of note, 4 (40%, 4/10) were found to have CMV VL of ≤500 IU/ml at the time of diagnosis of CMV disease.

Seven patients with CMV disease had underlying haematological malignancy and the majority of these were patients diagnosed with B-cell LPD (n=3) and multiple myeloma (n=3). One was heavily pretreated with eight previous lines of therapy. A patient with newly diagnosed AML developed CMV colitis after receiving the first cycle of chemotherapy. Despite not being significantly pretreated, the remission induction phase of chemotherapy was complicated by polymicrobial sepsis and prolonged ICU admission requiring systemic corticosteroids.

All three patients with solid organ malignancy developed CMV colitis post treatment with immune checkpoint inhibitors (ICI). They had immune-related adverse events (irAE) complicating ICI administration which required high dose corticosteroids and immunomodulatory drugs such as infliximab. Of 2018 patients receiving immune checkpoint inhibitors throughout this study period, 3 of 79 patients (3.8%) with steroid-refractory checkpoint inhibitor-induced colitis were diagnosed with CMV colitis.

Outcomes

The overall all-cause mortality within 12 months of CMV diagnosis was 37% (23/62). These deaths occurred at a median of 55 days (range, 3-250 days) following diagnosis of CMV DNAemia and/or disease. No deaths were directly attributed to CMV infection. Sixteen (16/23,

70%) succumbed due to progression of primary disease while the remaining (7/23, 30%) were due to nosocomial infections.

Discussion

We report the epidemiology of CMV DNAemia and disease in a non-allogeneic transplant cohort receiving current-era treatment regimens for malignancy. Importantly, we identified that patients with underlying haematological malignancy (particularly B and T-cell LPD, chronic lymphocytic leukemia, and multiple myeloma) were frequently observed to have CMV DNAemia and/or disease. Lymphopenia, multiple cancer therapies, co-infection, and recent use of systemic corticosteroids were commonly observed in this population. We acknowledge that the higher cumulative incidence of CMV diagnosis in the LPD patient cohort was partially driven by the use of alemtuzumab therapy in patients with cutaneous T-cell lymphoma. Alemtuzumab was frequently used for patients with Sezary syndrome during the early study period, but use has diminished since 2017 due to the availability of alternative (less immunosuppressive) treatment options.

Consistent with previous reports (6-10), we observed more CMV DNAemia in patients receiving alemtuzumab and idelalisib therapies. In fact, recognition of CMV infection following alemtuzumab and idelalisib has led to clinical guidelines for prospective monitoring of CMV DNA during treatment. (6, 8, 10-13) Apart from these therapies with known CMV risk, the magnitude of risk for CMV infection among other novel therapies is still largely undetermined and thus needs to be further evaluated.

BiTE antibody therapy is one of the novel immunotherapeutic agents being used in the treatment of relapsed or refractory ALL, diffuse large B-cell lymphoma (DLBCL) and myeloma. (14) Our study reported 3/62 cases of CMV DNAemia and/or disease following BiTE antibody

therapy in which one was complicated by CMV end-organ disease. BiTE antibody therapy has been shown to induce B-cell depletion and cause hypogammaglobulinemia but opportunistic infections such as CMV have been reported rarely in clinical trials. (15, 16) Currently available data do not suggest an association between BiTE antibody therapy and CMV infection. CMV infection is believed to be related to underlying host immunosuppression rather than therapy itself. (15-17) However, post-marketing data regarding BiTE and CMV diagnosis are sparse and real-world observation (such as current study) has demonstrated the possibility of developing CMV DNAemia and/or disease following BiTE therapy.

We also observed two patients who developed CMV DNAemia after grade 3 and 4 CRS following infusion of CAR T-cell. Interestingly, Wudhikarn and colleagues recently reported two cases of CMV DNAemia within the first 30 days of CAR T-cell infusion, in a cohort of patients where 80% developed cytokine release syndrome (CRS). (18) These real-world observations suggest that CMV DNAemia may occur early after CAR T-cell infusion, especially in the presence of CAR T-related toxicities. Severity of CRS and use of corticosteroids for the management of CRS were described as predictors of infection but the specifics of infection have not been well defined. (18-20). Furthermore, both cases in our cohort received fludarabine conditioning prior to CAR T-cell infusion. Lymphodepletion and resultant reduction in T-cell numbers after fludarabine has long been suggested as one of the potential risk factors for CMV in patients with hematologic malignancies not undergoing HCT. (21)

Immune checkpoint inhibitors alone were not expected to increase the risk of CMV DNAemia and/or disease as they promote T-cell effector function. (22) This is consistent with a low cumulative incidence (0.3%) of CMV diagnosis described in our study. Rather, high dose corticosteroids and immunomodulatory drugs used in the treatment of immune-related adverse

events (irAE) have been shown to increase the susceptibility of CMV infections. (23) To date, data on the incidence of CMV colitis in steroid-refractory autoimmune colitis is limited and our study showed that 3.8% of patients with steroid-refractory immune colitis developed CMV colitis. Clinicians caring for these patients should have a lower threshold for investigation of CMV colitis, particularly when there is a poor clinical response to steroids and/or TNF-alpha-targeted agents. Repeat diagnostic colonoscopy with tissue biopsies may be necessary to detect CMV colitis before further escalating immunosuppressive therapy. (24) When there is diagnostic uncertainty, a multidisciplinary approach involving infectious disease specialist and gastroenterologist is advised. (22)

Although currently available data from clinical trials of novel therapies do not report an association with CMV infection, cases of CMV DNAemia and disease in post-marketing real-world studies are increasingly reported. This should spark vigilance for CMV diagnosis, especially in situations like irAE or CRS where immunomodulatory drugs and high dose corticosteroids are required.

Clinical implications of CMV DNAemia in cancer patients other than allogeneic HCT

We observed that all patients with CMV disease in our study had concurrent CMV DNAemia, reflecting high sensitivity for the detection of CMV infection via PCR testing. In other settings, quantification of CMV DNA correlates with disease and infection severity (25) However, the use of CMV DNA from blood specimens to predict CMV disease has not been prospectively validated in this non-transplant patient group where the incidence of CMV disease is considered low. (26)

Caution must be exercised when interpreting a negative or low-level CMV DNAemia in symptomatic patients as this may not completely exclude CMV disease. Variation in timing and

frequency of CMV testing could impact upon results and tissue sampling for histopathological testing is therefore imperative in patients with high clinical suspicion of CMV disease. On the other hand, in asymptomatic patients with CMV DNAemia, monitoring of CMV VL trends rather than pre-emptive treatment would appear to be a valid approach as a treatment in this situation could infer more risks than benefits to patients. Furthermore, our study and others have shown that this group of patients may not develop CMV disease. (8) Anti-CMV therapy could be considered when the patient becomes symptomatic, having high CMV VL or rising trends of VL. (25, 27)

Our study is limited by the retrospective, single-center study design, and small sample size. Furthermore, pre-treatment CMV serology status was not routinely assessed in all patients particularly those with solid organ malignancy and CMV testing was at the discretion of the treating physician rather than routine practice. As a result, the cumulative incidence of CMV DNAemia and/or disease in each subgroup of therapy (except alemtuzumab) may be under-estimated.

Conclusion

Patients with hematological malignancy particularly B and T-cell LPD, CLL, and multiple myeloma, together with clinical characteristics such as lymphopenia, multiple cancer therapies, co-infection and treatment with high doses of systemic corticosteroids, could potentially pose an increased risk for CMV DNAemia and disease. Presence of these features should prompt testing for CMV. Future prospective studies are necessary to determine strategies for optimal diagnosis and management of CMV in these patients.

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Authors' contributions: KHT and MKY are responsible for the concept and design of the study, data analysis, and interpretations; KHT is also responsible for the acquisition of the data and manuscript writing; KHT, MKY, MS, JC, LW, BWT, AK, CST, and KT were involved in the discussion and final critical revision of the manuscript.

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The authors declare no potential conflicts of interest.

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