Cytomegalovirus Reactivation in Adult Acute Lymphoblastic Leukemia Patients during POMP Maintenance Chemotherapy: Do We Underestimate the Dormant Virus?

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Introduction

- Cytomegalovirus (CMV) is a common herpes virus that infects around 60-100% of adults, and is one of the most common pathogens involved in infectious complications post- hematopoietic stem cell transplantation (HSCT).
- Infections with the CMV can cause complications such as pneumonia, retinitis, and enterocolitis.
- Studies have shown that HSCT patients are at higher risk for CMV reactivation leading to disease and have high morbidity and mortality rates.
- Nevertheless, CMV infections have been reported in non-transplant patients, especially in the pediatric population.
- There are several case reports that highlight the complications of CMV in non-transplant acute lymphoblastic leukemia (ALL) pediatric patients.
- Very few cases of CMV infections have been reported in non-transplanted adult ALL patients during maintenance chemotherapy.

Objective

To report a case series on adult ALL, non-transplant patients with CMV disease

Methods

▪We report four adult patients who were diagnosed with ALL at the American University of Beirut Medical Center (AUBMC), Lebanon, achieved complete remission after induction chemotherapy without HSCT and then developed CMV disease during their maintenance chemotherapy treatment with POMP protocol:

- ▪Mercaptopurine
- ▪Vincristine
- ▪Methotrexate
- ▪Prednisone.

Results

- Four cases of ALL patients (all were males, age range from 20 to 73 years) are reported (table 1).
- Patient 1 presented with sequential vision loss at 5th month of POMP treatment.
- Patient 2 presented with fever and diarrhea at 2nd month of POMP treatment.
- Patient 3 presented with fever, diarrhea and respiratory distress at 11th month of POMP treatment.
- Patient 4 presented with respiratory distress at 8th month of POMP treatment.
- Three patients cleared CMV viremia after first line treatment with either ganciclovir or valganciclovir, whereas one patient required second line treatment with Ganciclovir, Foscarnet and intravenous immune globulin.

Patient	Age (yrs)	Risk category	Presenting symptoms	CMV Viremia	Time of CMV Disease	Disease	Treatment	Medications	Outcome
1	42	SR (B-ALL)	Sequential vision loss	+	5th month of maintenance	CMV retinitis	1st line	Ganciclovir	Residual visual impairment
2	55	SR (B-ALL)	Fever, diarrhea	+	2nd month of maintenance	CMV viremia	1st line	Valgancicl-ovir	Resolution of viremia and diarrhea, death due to other cause
3	73	SR (pre-B ALL)	Fever, diarrhea, respiratory distress	+	11th month of maintenance	CMV colitis, CMV pneum-onia	1st line 2nd line	Ganciclovir Ganciclovir Foscarnet IVIG	Resolution of symptoms with persistent viremia
4	20	SR (T-ALL)	Respiratory distress	+	8th month of maintenance	CMV pneum-onia	1st line	Valgancicl-ovir	Complete response

Table 1. Patients' characteristics and details
Abbreviations: yrs: years; SR: standard risk; ALL, acute lymphoblastic leukemia, + Present

Discussion

▪To the best of our knowledge, the majority of CMV infections in patients on maintenance treatment are reported to be in childhood ALL.

▪This makes our case series the first of its type to report these cases of CMV infections in adult patients with ALL while on maintenance treatment.

▪The maintenance regimens used in the treatment of adult ALL patients are similar to those used in the treatment of pediatric ALL patients (including 6-mecaptopurine, methotrexate, vincristine, and steroids).

▪A suggested mechanism for CMV reactivation is due to the profound immunosuppression that develops after having low ALC, CD4 + T-cell count, and immunoglobulin levels in the maintenance period.

▪Depletion of lymphocytes during maintenance phase may play a significant role in CMV reactivation. Lymphopenia may contribute to more prevalent CMV reactivation during this phase rather than in the induction or consolidation phases as a result of two possible causes: (1) drugs given during maintenance phase, and (2) CMV reactivation itself causing cytopenia hindering subsequent CMV clearance

▪It is not mandatory to have high-level CMV DNAemia to develop organ involvement, especially in patients who are post-transplant or on chemotherapy.

▪There is no consensus on the monitoring of CMV status during ALL therapy.

▪For adult patients treated with pediatric inspired ALL regimens, CMV reactivation seems to be an emerging problem and may be under-recognized.

▪Monitoring for CMV infection surveillance by CMV DNA PCR in the pediatrics population with ALL during the maintenance phase especially if the absolute lymphocyte count (ALC) is low (<800 lymphocytes/μL) is suggested for adult ALL patients especially that maintenance regimens are mostly inspired from the pediatrics regimens and similar drugs are used.

Conclusions

- Our observations and a review of the literature suggest this is a rare entity with potentially high morbidity.
- The majority of patients develop asymptomatic viremia before manifestations of end-organ damage.
- Clinicians shall be aware of this entity especially in patients who are at high risk for developing CMV reactivation and disease such as those with positive serology and prolonged lymphopenia, which is commonly encountered during the maintenance treatment.

Disclosures

▪All authors have no conflict of interest.

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