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Case Report

Cytomegalovirus reactivation during adult acute lymphoblastic leukemia maintenance: do we underestimate (un)expected guest of pediatric approach?

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Abstract: Among acute lymphoblastic leukemia (ALL), 40% of affected patients are diagnosed after the age of 20. Compared to pediatricians, adult hemato-oncologists are less familiar with complex pediatric ALL regimens and have perceived that pediatric ALL regimens are too toxic in the adult population. Meanwhile, multiple retrospective analyzes showed the superiority of pediatric regimens among the older adults and young adolescents (AYAs) group over adult regimens. A series of prospective studies have made it apparent that pediatric-inspired ALL regimens are feasible in AYAs, with manageable toxicities and potentially more encouraging results. However, the complications in the adult population are still to be explored. Although cytomegalovirus (CMV) viremia and infections are increasingly recognized in pediatric ALL cases, we generally do not experience it frequently in adult cases with conventional strategies. Herein we represent a 38-year-old man diagnosed with ALL and treated with pediatric inspired GRAALL-2003 protocol. Following a successful induction phase, he had pancytopenia, deep lymphopenia, fever and diarrhea in the 9th month of maintenance therapy. With increased serum ferritin and triglyceride levels, he had features of macrophage activation syndrome. The bone marrow biopsy did not reveal any relapse or hemophagocytosis. We detected highly increased levels of CMV DNA (657.262 copies/mL) in blood analysis.

Keywords: Acute lymphoblastic leukemia, adolescent and young adults, pediatric protocols, cytomegalovirus reactivation, macrophage activation syndrome

Introduction

Among acute lymphoblastic leukemia (ALL), 40% of affected patients are diagnosed after the age of 20 [1]. Multiple retrospective analyzes showed the superiority of pediatric regimens among the older adults and young adolescents (AYAs) group over adult regimens [2]. Pediatric approach includes higher doses of asparaginase, vincristine, steroid and cumulative intrathecal therapy compared to adult approach, followed by extended (2 to 3 years) maintenance therapy. A series of prospective studies have made it apparent that pediatric-inspired ALL regimens are feasible in AYAs, with manageable toxicities and potentially more encouraging results [2-7].

Although cytomegalovirus (CMV) viremia and infections are increasingly recognized in pediatric ALL cases [8], it is not frequently experienced in adult cases treated with GMALL protocols [9]. Actually, CMV infection is a significant cause of morbidity and mortality in the post-transplant setting for adult hemato-oncologists [10]. In the maintenance phase of ALL treatment protocols, the immunosuppression is lighter compared to induction phases and CMV DNA are not monitored as CMV infections are not expected. Herein we represent a case that has been treated with pediatric inspired regimen as being in AYA group, and had CMV reactivation with features of macrophage activation syndrome in the maintenance phase of his treatments. Written informed consent was

Table 1. Laboratory values at the time of Cytomegalovirus reactivation

	Values at the time of CMV reactivation	Normal
White blood cells	3510/μl	4300-10300/μl
Lymphocytes	140/μl	1200-3600/μl
Hemoglobin	10.9 g/dl	13.6-17.2 g/dl
Thrombocytes	95.000/μl	155-375.000/μl
Prothrombine time	14.22 sec	10-15 sec
INR	1.24	0.85-1.2
Activated partial thromboplastin time	25.77 sec	21-36 sec
Fibrinogen	110 mg/dl	180-350 mg/dl
LDH	408 U/L	<250 U/L
Ferritin	2000 ng/ml	30-400 ng/ml
Triglycerides	331 mg/dl	<150 mg/dl
Cytomegalovirus DNA	657.262 copies/ml	

attained from the patient and the publication of the case was approved by local ethical committee.

Case report

A 38 year-old male patients has been diagnosed as having B-cell ALL. A WBC count of 36100/μl was as baseline high-risk factor. He had no cytogenetic abnormality. A pediatric-inspired therapy for adults with Philadelphia chromosome-negative ALL according to the GRAALL-2003 study was started (6). He achieved complete response (CR) after the first induction course. The response-based high-risk factors were not completed with minimal residual disease (MRD) measurement due to technical failure. He completed the consolidation blocks of 1 to 6 according to the protocol and commenced on maintenance with central nervous system irradiation. Maintenance treatment included methotrexate (MTX; orally 25 mg/m^2/wk for 24 months), 6-mercaptopurine (6-MP; 60 mg/m^2/d for 24 months), vincristine (VCR: 2 mg on day 1 monthly for 12 months), prednisone (PDN; 40 mg/m^2/d on days 1-7 monthly for 12 months). At the 9th month of the maintenance, he presented with fever, and diarrhea. He had pancytopenia with striking lymphopenia (**Table 1**). Serum LDH level was found to be increased and ALL relapse was suspected. The increase of serum ferritin level with hypertriglyceridemia and low fibrinogen level pointed to association of macrophage activation syndrome. Broad spectrum antibiotics were started intravenously (iv) and fresh frozen plasmas were given as replacement. Bone marrow aspiration did not reveal relapse and hemaphagocytosis. His pancytopenia deepened rapidly as WBC dropped to 1000/μ and platelets to 45.000/μl. Dexamethasone was added. Meanwhile, serum CMV DNAemia was found to be 657.262 copies/mL. To clarify whether the diarrhea was related to CMV colitis or not, colonoscopy was planned but could not be performed due to poor performance status. Although the standard of care is iv gancyclovir, the drug was not accessible that time in the country and we started oral valgancyclovir 900 mg bid (1800 mg/day). The diarrhea regressed at the second week. The CMV DNAemia disappeared at the end of 2nd month of valgancyclovir treatment.

With improved cell counts ALL maintenance protocol restarted under valgancyclovir maintenance. He is still on ALL maintenance as being at 18th month and did not experience any new CMV reactivation event.

Discussion

Cytomegalovirus (CMV) is prevalent worldwide and is usually acquired during childhood. In Turkey, among adult patients the seroprevalence of CMV infection is around 97% [11]. It is a latent virus and activation can occur after immunosuppression [12]. While the humoral and innate immune responses play a role in the early phase of infection, cellular immunity is required to control its latency, prevent reactivation, and inhibit progression to disease [13]. The CMV disease is a major cause of death in stem cell and organ transplant recipients and

Table 2. Summary of CMV reactivation in the maintenance phase of pediatric case series

	n	median age (range)	Phase of chemotherapy	median viral load (range)	Signs and symptoms	Presence of lymphopenia	End organ damage	Treatment	Outcome
Phasuk et al. [8]	8	9 (4-16)	Maintenance <1 year (n=1)	13.857 copies/ml	Asymptomatic (n=7)	ALC<1500/mcl in 7 patients	Hepatitis (n=5)	Ganciclovir or valganciclovir (n=5)	Virus suppressed (n=7), however one patient expired 2 weeks later due to septicemiaral load was 723 copies/ml in one case at the time of analysis.
			Maintenance ≥1 year (n=7)	(1994-1.307.730)	Febrile neutropenia (n=1)		Retinitis (n=1)	No medical intervention (n=3)	
Jain et al. [15]	10	6 (2-12)	Maintenance <1 year (n=6)	495.000 copies/ml (0-28*10^6)	Prolonged febrile neutropenia (n=6)	Present in 9 patiens; median was 488/mcl	Eye (n=5)	Ganciclovir or valganciclovir (n=9)	The case who had supportive treatment died due to pneumonia
			Maintenance ≥1 year (n=4)	Negative in 2 cases and below the limits of determination in 1 case; all 3 had end organ disease	Hemophagocytic lymphohistiocytosis (n=1)		Lung (n=4)	Supportive (n=1)	Other seven cases survived; four experenced recurrence of CMV
							GIT (n=2)	IVIG (n=3)	
							HLH (n=1)	Intravitreal gancyclovir (n=3)	
							>1 organ involved in 3 cases	Vitrectomy (n=1)	
								Methylprednisolone (n=1)	
Rahbarimanesh et al. [16]	4	11.5 (3-15)	Maintenance <1 year (n=1)	1.010.125 (328.000-1.600.000)	Fever (n=9)	ALC<800/mcl (n=3)	Hepatosplenic (n=2)	Oral valganciclovir (n=4)	All cases had full resolution
			Maintenance ≥1 year (n=3)			ALC=1100/mcl in one case	Pneumonitis (n=1)		
							Eye (n=1)		

CMV: Cytomegalovirus, ALC: Absolute lymphocyte count, HLH: Hemophagocytic Lymphohistiocytosis, IVIG: Intravenous immunoglobulin.

people with AIDS. Our patient did not undergo stem cell transplantation and did not have AIDS. Data in adult patients with cancer and leukemia who have not undergone transplantation are scanty [14].

Our patient has deep lymphopenia in addition to macrophage activation at the time of CMV reactivation (**Table 1**) within the first year of ALL maintenance therapy. Review of the literature revealed emerging CMV reactivation experiences especially in pediatric ALL patients, mostly associated with cytopenia (**Table 2**). In the single center, cross-sectional study including 50 pediatric non-transplant ALL cases, differing from other trials, authors planned to monitor the CMV status of the patients and finally reported that CMV viremia prevalence was indeed 52% [8]. All of them had positive CMV serology at baseline. Eight patients with high CMV viremia defined as over 1000 copies/ml. All of them were in the maintenance phase of chemotherapy and 7 of them were over the first year of maintenance. At the time of reactivation, 7 patients had ALC less than 1000/mm^3. The ROC curve analysis showed that ALC <798/mm^3 discriminated high level from low level CMV viremia [8]. Similarly, Jain et al. reported that 10 cases in the maintenance phase of treatment experienced CMV reactivation. The median lymphocyte coun was 488/mcl at presentation and one case had hemophagocytic lymphohistiocytosis [15]. In another report including 4 patients, three cases had lymphocyte count <800/mcl at the presentation [16]. These results are in accordance of our patient's presentation.

It is clear that 6MP/MTX maintenance treatment may cause myelosupression and, the resulting cytopenia is challenging for discrimination whether it is related with drug adverse event or relapse. In this stage, we advise inclusion of CMV reactivation in differential diagnosis. Indeed, CMV reactivation was reported in pediatric patients essentially during nonintense phase of chemotherapy, mostly in the maintenance phase of protocols [8]. For our patient, the lymphopenia level was the key as being as 140/mm^3. However, whether the lymphopenia causes CMV reactivation or the reactivation causes lymphopenia is an open room for discussion. Additionally, determination of CMV viremia with features of macrophage activation syndrome is not frequent. The immunologic mechanism of the CMV reactivation in the maintenance phase of protocol needs further investigation.

In conclusion, there is not a 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 underrecognized. ALL patients who are on the maintenance phase and have low ALC counts should be assessed for CMV reactivation and related end-organ disease.

Disclosure of conflict of interest

None.

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