Prevalence of Epstein-Barr Virus infection in a cohort of onco-hematologic paediatric patients

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Background & Aim

- *Epstein-Barr Virus (*EBV) is associated with an increased risk in term of morbidity and failing of therapeutic strategies in onco-hematologic disorders.
- Post-transplant lymphoproliferative disorder (PTLD) represents a spectrum of lymphoproliferative disorders and is a serious complication of paediatric transplantation.
- The majority of PTLD are associated with **Epstein Barr virus** (EBV) and the characteristic EBV+ B cell lymphomas are the leading **post-transplant malignancy in children**. EBV+ PTLD remains a formidable issue in pediatric transplantation and is thought to result from impaired immunity to EBV as a result of immunosuppression. However, the key viral and immune factors that determine whether EBV+ PTLD develops remain unknown.

Here, we evaluate the prevalence of EBV infection in paediatric patients (pts) with Acute Leukemia after Hematopoietic Stem Cell Transplant (HSCT).

Material & Methods

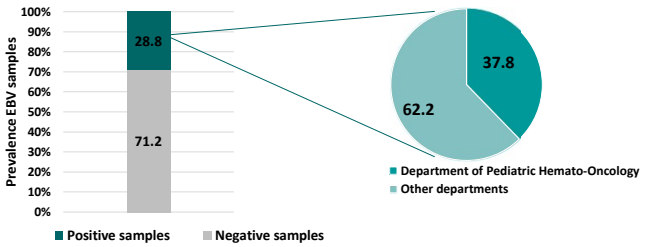
- From October 2021 to October 2022, patients referred to the department of Hematology/Oncology, Cell and Gene Therapy, were tested for quantification of EBV-DNAemia in case of evaluation of EBV infection or reactivation as well as active surveillance after HSCT, at Virology Laboratory of Diagnostic Microbiology and Immunology Unit at Bambino Gesù Children's Hospital-IRCCS (Rome, Italy).
- Patients with clinical information available were selected for a retrospective analysis and classified according to subtypes of onco-hematological disease: (i) Acute Lymphoblastic or Myeloid Leukemia (ALL-T, ALL-B, AML), (ii) lymphoma, (iii) non-malignant haematology disorder and (iv) solid organ transplant (SOT).
- Epstein-Barr Virus DNA was extracted from whole blood (WB) samples using the QIAsymphony DNA Mini Kit (QIAGEN, Hamburg, Germany). EBV amplification, based on real-time PCR technology, was performed with **ARTUS EBV PCR kits (Qiagen).**

Results

Patients' characteristics

From October 2021 to October 2022, 13650 blood samples from 3199 patients were tested for quantification of EBV-DNAemia both as diagnosis of (re)-activation of EBV infection at IRCCS Bambino Gesù Children's Hospital (Rome, Italy). Among them, 28.8% (3931/13650) resulted positive.

Most of EBV positive samples resulted from individuals referred to the department of Hematology/Oncology, Cell and Gene Therapy.



Considering the higher EBV prevalence in the onco-hematologic setting we focused our analysis only in this population.

Paediatric onco-hematologic population

In the analysis period, among 667 paediatric onco-ematologic patients tested for quantification of EBV-DNAemia a total of 232/667 (34.8%) patients had at least one EBV positive blood sample, with a median (IQR) EBV-DNAemia of 2150 (439-9733) cp/mL at onset. They were mainly males (126/235, 54.3%), with a median (IQR) age of 8.3 (5.1-14.9) years.

Distribution of onco-hematologic malignancy

The prevalence of EBV infection was higher in those with Acute Lymphoblastic or Myeloid Leukemia (109/232, 47%) than in the other subtypes of malignancy (non-malignant haematology disorder [93/232, 40.1%], solid organ transplant [17/232, 7.3%] and lymphoma [13/232, 5.6%]).

Acute Leukemia

47 %	I) Acute Lymphoblastic or Myeloid Leukemia (ALL-T, ALL-B, AML)
40.1 %	II) Hematologic Disease NOT Malignant
7.3 %	III) Solid tumor
5.6 %	IV) Lymphoma (Hematologic Malignant)

By focusing on patients with Acute Leukemia, 60/109 were males (55%) and 49/109 females (45%), with a median (IQR) age at EBV onset of 8.4 (5.6-14.8) Years. The selected pats had a median (IQR) EBV-DNAemia of 1343 (315-5330) cp/mL at onset and a median (IQR) peak of infection of 8319 (1995-34181) cp/mL. Among those, 69/109 (63.3%) underwent a Hematopoietic Stem Cell Transplantation (HSCT). Graft versus Host Disease was reported in 9/35 (25.7%) patients with available informations.

Disease	
Acute Lymphoblastic Leukemia (ALL)	**76 (69.7)**
Acute Myeloid Leukemia (LAM)	32 (29.4)
Acute Promyelocytic Leukemia (APL)	1 (0.9)
HSC* trasplant	69 (63.3)
Haploidentical	34 (31.2)
Matched Unrelated Donor (MUD)	32 (29.4)
Unknown	4 (3.7)
Median (IQR) age at EBV onset, years	11.2 (6.5-15.3)
Median (IQR) age at transplantation, years	8.9 (5.7-14.0)

*Hematopoietic Stem Cell Transplantation

In the transplant population, the median (IQR) of duration of infection was 25 (0-82.6) days, while the median time from transplantation to onset of EBV infection was 115 (50-476) days.

There were a significant differences between the median (IQR) age at EBV onset and the age at HSC-transplantation (p>0.001).

Conclusions

Acute lymphoblastic leukemia (ALL) is one of the most common malignant diseases of the hematopoietic system in children. Although the etiology of ALL is unknown, it has been reported that it may be associated with Epstein-Barr virus (EBV) infection associated with poorer overall survival rate and shorter survival. In good clinical practice, EBV reactivation in peripheral blood is routinely monitored in immunocompromised patients by quantitative EBV-DNAemia.

In this study, we analyzed the impact of EBV infection in childhood AL affected at largest pediatric oncohematology referral center in Italy. This study reports one year of the experience in monitoring EBV showing high prevalence of EBV infection in paediatric onco-hematologic patients, with a diagnosis of Acute Leukemia. Surprisingly, in the period analyzed, EBV infection to occur beyond 100 days post HSC transplantation. Monitoring EBV by viral load and defining time-window for early diagnosis of EBV may play an important role for proper strategy of management of onco-hematologic patients.