EPSTEIN-BARR VIRUS INFECTION IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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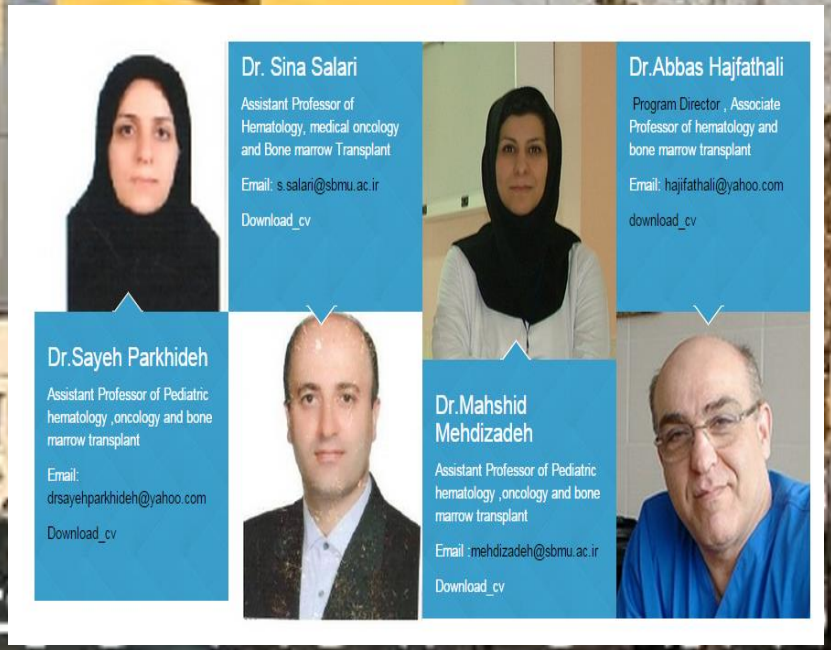

CASE 1

- A 10 years old thalassemic boy on day +28 admitted with fever ,generalized edema pneumonia and mild pleuresis
- Evaluation for bacterial and fungal and CMV were negative ,EBV viral load was 1580 copy/µl
- Repeated EBV viral loads were 1700copy/µl
- We reduced the dose of CSA and continue supportive care,monitor the EBV
- During next 2 weeks the viral load decreased and the symptoms gradually disappeared

CASE 1

- Be monitored for EBV up to one year
- 5 years later free of thalassemia, No PTLD

CASE 2

- 23 years old male patients with ALL CR2 under went MRD allo transplant
- No acuteGVHD ,no chronic GVHD
- He had two hospital admission in first and second post transplant year (first for fever and then due to pancytopenia)
- No EBV monitoring
- He had bone pain 4 years after transplant, NL BM,STR>98 ,RF ++,elevated ESR,he was referred to rheumatologist,c GVHD??
- One year later : no response to treatment,positive bone scan,NL BM,NL STR ,Bone biopsy showed DLBL ,diagnosed as PTLD

EBV IN HSCT

- Epstein - Barr virus (EBV) is a gamma - herpes virus that infects 50-89% of children and remains latent, in
memory B cells, of ~90% of adults .

- Most EBV primary infections and reactivations are subclinical and require no therapy in immunocompetent people.

- EBV infection or reactivation may result in life-threatening diseases in immunocompromised people

EBV IN HSCT

- Hematopoietic stem cell transplants is an effective therapy in the treatment of hematological malignancies
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- The iatrogenic suppression of T-cell with the immunosuppression of the transplant regimens, allows the proliferation of infected B cells

EBV IN HSCT

- The incidence of EBV DNAemia varies within transplant centers, ranging from 0.1 to 63%
- there are significant differences amongst transplant centers that may be explored considering the individual characteristics of patients.
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- EBV infection is most common within the first 100 days post-transplant, in high-risk patients

HIGH-RISK PATIENTS FOR EBV INFECTION

- T-cell depletion
- EBV serology donor/recipient mismatched
- cord blood transplantation
- HLA mismatch
- Splenectomy
- second HSCT
- severe acute or cGVHD and high or rising EBV DNAemia
- the use of ATG
- unrelated donor
- Myeloabelative conditioning regimens versus RIC

ATG AND EBV

- beneficial effects in preventing GVHD,
- It delays immune reconstitution, promoting an increased risk of EBV reactivation, and PTLD
- higher doses of ATG seem to be related with PTLD development

GVHD AND EBV

- GVHD is related to delayed immune reconstitution, favoring infections in the early period post-transplant.

- viral infections are also associated with delayed immune response and appear to be linked to the degree of immunosuppression

TIMING OF EBV INFECION

- unrelated donor, myeloablation and the use of ATG
  seem to be risk factors for EBV infection occurrence at D+60
- GVHD is connected to EBV infection at D+90
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- ATG,unrelated donor and GVHD are related to EBV infection at day D+150

EBV MONITORING

- Should be by quantitative PCR
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- must start at the first month post-transplant
- should be performed at least during 4 months after transplantation

EBV DNA LOAD

- EBV-DNA loads of blood are acted as the main basis for diagnosis,preemptive therapy and therapeutic evaluation
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- Special EBV-associated disease in CNS and pulmonary had the discrepancy in EBV-DNA loads

- patients with isolated EBV-associated CNS PTLD
  might be the cerebrospinal fluid (CSF) EBV-DNA positive, but blood EBV-DNA negative.

CLINICAL PRESENTATIONS

- EBV is associated with a spectrum of clinical presentations from fever to post-transplant lymphoproliferative diseases (PTLD)

- EBV can involve nearly all other tissues and organs in recipients of transplants other than lymph nodes(isolated central nervous system involvement with PTLD is an exceedingly rare complication after alloHSCT)
- viremia
- Pneumonia
- encephalitis/ myelitis
- enteritis accompanying hepatitis PTLD 0.5% to 22%
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- Kinch et al.

THE TREATMENT OF EBV-ASSOCIATED DISEASES

- rituximab (AII)
- reducing immunosuppression (BII)
- donor lymphocyte infusion (DLI) (CIII)
- donor EBV specific cytotoxic T cells (CTL) infusion (CII)
- chemotherapy (CIII)

- The initial response rates of administration of rituximab to EBV-associated diseases ranged from 39.2%
  to 100%

TREATMENT

- Considering low morbidity and mortality of EBV-associated disease
- Prempetive therapy
- Rituximab
- manipulate the immune system to target and eradicate the viremia
- the balance toward EBV immune responses either by depleting the B-cell population (including EBV-infected B cells) or by augmenting the cellular immune response to EBV

- is used prophylactically before or shortly after transplant to reduce the risk ofEBV DNAemia and PTLD development in high-risk patients, such as patients with EBV-seropositive donors

TREATMENT

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- EBV-specific CTL acts as the best treatment of EBV-associated diseases but currently iso experimental protocols
- DLI, chemotherapy, have a limited place
- Antiviral agents (EIII) and intravenous immune globulin (IGIV) (DIII) are not recommended
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POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

- occurs within the first 6 months following alloHCT prior to effective reconstitution of cytotoxic T lymphocytes needed to prevent EBV-mediated, B-cell transformation into lymphoblasts.

- PTLD can be EBV negative potentially induced by other viral reactivation

- Incidence is 224, 54, and 31 per 100,000 transplants during the first, second, and sixth year following transplantation
- Overall, PTLD occurred in 1% of alloHCT
- One year survival of patients who developed PTLD was 53% (47-59%).
- no difference in OS between EBVpos and EBV neg PTLD

PTLD

432 cases of PTLD following alloHCT from 2002-2014
78% received ATG or alemtuzumab.
PTLD was highest in umbilical cord and lowest in MRD
There was no impact on survival by EBV-status in multivariable analysis
There is no difference in survival outcomes for patients with EBVpos or EBVneg PTLD
PTLD occurring following alloHCT and 1-year survival is poor. Features of conditioning and use ofserotherapy remain important.

Article type : Original Report

Survival Outcomes of Allogeneic Hematopoietic Cell Transplants with EBV positive or EBV negative Post Transplant Lymphoproliferative Disorder (PTLD), A CIBMTR Study.

Seema Naik MD[1*], Marcie Riches MD, MS[2*], Parameswaran Hari MD[3], Soyoung Kim PhD[3,4], Min Chen MS[3], Carlos Bachier MD[5], Paul Shaughnessy MD[6], Joshua Hill MD[7], Per Ljungman MD[8], Minoo Battiwalla MD[5], Saurabh Chhabra MD[9], Andrew Daly MD[10], Jan Storek MD[11], Celalettin Ustun MD[12], Miguel Angel Diaz MD[13], Jan Cerny MD[14], Amer Beitinjaneh MD[15], Jean Yared MD[16], Valerie Brown MD[17], Kristin Page MD[18], Parastoo B. Dahi MD[19], Siddhartha Ganguly MD[20], Sachiko Seo MD[21], Nelson Chao MD[22], Cesar O. Freytes MD[6], Ayman Saad MD[23], Bipin N. Savani, MD[24], Kwang Woo Ahn PhD[3,4], ,Michael Boeckh MD[26], Helen E Heslop MD[27], Hillard M. Lazarus MD[28], Jeffery J. Auletta, MD[25†], Rammurti T Kamble MD[27†]

PATHOLOGY

- PTLD represents a heterogeneous group of non-Hodgkin's lymphomas histologically classified as polymorphic or monomorphic

- DLBCL, Burkitt lymphoma, Burkitt-like lymphoma, and Hodgkin-like lymphoma.

RISK FACTORS

- T-cell depletion especially via *ex vivo* methodology even up to 29%
- unrelated or (HLA)-mismatched related donor
- use of ATG (RR= 6.4, $p<0.001$) or anti-CD3 monoclonal antibody (RR=43.2, $p<0.001$)
- grades II-IV aGvHD
- Extensive cGvHD
- conditioning regimens that included radiation
- EBV serostatus
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DIFFERENCES BETWEEN SOLID ORGAN TRANSPLANT (SOT) RELATED AND ALLOHCT-RELATED PTLD

- There are notable
  and the incidence and outcomes of PTLD varies markedly
- In HSCT earlier, has an aggressive course and poorer survival

PTLD PROGNOSIS

- Late PTLD (>6 months after alloHCT) was reported in 11%

- Age at alloHCT (>30 years), extra nodal involvement, aGvHD greater than grade II, and absence of reduction in immunosuppression as poor prognostic factors.

IN CONCLUSION

- EBV infection or reactivation can present as a variety of clinical symptoms and signs, and involve nearly all tissues and organs
- EBV-DNA monitoring of blood is a routine method for diagnosis of PTLD and acted as an important indicator for preemptive therapy and therapeutic evaluation.
- The preemptive use of rituximab can reduce the risk of death due to EBV PTLD in allo-HSCT.
- The question of over treatment to Select candidates for pre-emptive treatment in order to avoid systematic anti-CD20 treatment

REVIEW

Management of post-transplant lymphoproliferative disorders

Gabriela Llaurador[a], Lauren McLaughlin[b], and Birte Wistinghausen[a]

Purpose of review
Post-transplant lymphoproliferative disease (PTLD) is a major complication of hematopoietic stem cell and solid organ transplantation. The incidence of transplantation in childhood has been steadily rising, making
The purpose of this review is to

Bone Marrow Transplantation
https://doi.org/10.1038/s41409-019-0548-7

REVIEW ARTICLE

Epstein-Barr virus-related post-transplant lymphoproliferative disease (EBV-PTLD) in the setting of allogeneic stem cell transplantation: a comprehensive review from pathogenesis to forthcoming treatment modalities

Rama Al Hamed[1] · Abdul Hamid Bazarbachi[1] · Mohamad Mohty[1]

Received: 13 February 2019 / Revised: 10 April 2019 / Accepted: 15 April 2019

Wu and Liu *Journal of Hematology & Oncology* 2012, **5**(Suppl 1):A8
http://www.jhoonline.org/content/5/S1/A8

MEETING ABSTRACT Open Access

Epstein - Barr virus - associated Diseases in Allogeneic Hematopoietic Stem Cell Transplantation

Xiu-li Wu, Qi-fa Liu*

From New developments in Hematology and Oncology in 2011
Guangzhou, China. 25-26 December 2011

JCI The Journal of Clinical Investigation

Immunotherapy for transplantation-associated viral infections

Claire Roddie, Karl S. Peggs

J Clin Invest. 2017;127(7):2513-2522. https://doi.org/10.1172/JCI90599.