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B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Management of Epstein-Barr virus reactivation following allogeneic stem cell transplantation

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Summary

Background Epstein-Barr virus (EBV) reactivation is a frequent event (5–20%) following allogeneic stem cell transplantation (allo-SCT) that may progress to life-threatening EBV-lymphoproliferative disease (EBV-LPD).

Aim To present data relevant to incidence, diagnosis and contemporary management of Epstein-Barr virus (EBV) reactivation in children undergoing allogeneic haematopoietic stem cell transplantation.

Materials/Methods A review of PubMed references based on evidence-based recommendations and own experience

Results Epstein-Barr virus (EBV) reactivation is a frequent event (5–20%) following allogeneic stem cell transplantation that may progress to life-threatening EBV-lymphoproliferative disease (EBV-LPD), especially after T-cell depletion *in vitro* and/or *in vivo*. Clinical symptoms are frequently lacking in the early stages of EBV reactivation. The introduction of real-time polymerase chain reaction (RQ-PCR) several years ago has provided a powerful tool to monitor EBV reactivation in still asymptomatic allo-SCT recipients and to predict increased risk of developing EBV-LPD. Recently, evidence has been provided that EBV-DNA load guided preemptive treatment with B cell depleting CD20 monoclonal antibodies (Rituximab®) is effective in preventing EBV-LPD in allo-SCT recipients at high risk.

Conclusions We propose that simultaneous and on-line analysis of both EBV-DNA load and T cell recovery will improve the identification of patients at high risk for EBV-LPD. These patients will probably benefit most from pre-emptive interventions.

Key words **EBV reactivation • EBV-lymphoproliferative disease • allogeneic HSCT**

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Background

Allogeneic stem cell transplantation is increasingly used for the treatment of various benign and malignant haematological disorders, primary immunodeficiencies and metabolic diseases.

Epstein-Barr virus (EBV) reactivation is a frequent event (5–20%) following allogeneic stem cell transplantation (allo-SCT) that may progress to life-threatening EBV-lymphoproliferative disease (EBV-LPD)

Aim

To present data relevant to incidence, diagnosis and contemporary management of Epstein-Barr virus (EBV) reactivation in children undergoing allogeneic haematopoietic stem cell transplantation.

Materials and Methods

References were retrieved using the online database of the National Library of Medicine (PubMed; *http://www.ncbi.nlm.nih.gov/PubMed*). Terms used included: EBV reactivation, EBV-lymphoproliferative disease, allogeneic HSCT. The retrieved references were supplemented by references from the author's own database.

Results

Allogeneic stem cell transplantation is increasingly used for the treatment of various benign and malignant haematological disorders, primary immunodeficiencies and metabolic diseases

As a result of more accurate HLA typing, improved T cell depletion by graft manipulation *in vitro* and *in vivo*, and progress in supportive care, SCTs with unrelated and mismatched donors are increasingly performed and currently represent around 70% of paediatric SCTs. Inevitably, these types of SCTs are characterized by a prolonged period of immune incompetence post transplant. This lack of immune surveillance results in increased frequency, duration and severity of reactivation of human herpes viruses and adenoviruses.

Epstein-Barr virus (EBV) reactivation is a frequent event (5–20%) following allogeneic stem cell transplantation (allo-SCT) that may progress to life-threatening EBV-lymphoproliferative disease (EBV-LPD). Risk factors for EBV reactivation and subsequent EBV-LPD include the use of unrelated or mismatched family donors, T-cell depletion *in vitro*, anti-thymocyte globulin (ATG) and non-myeloablative SCTs [1].

Clinical symptoms are frequently lacking in the early stages of EBV reactivation and are often only recognized in the later stages where they coincide with progressive EBV-LPD. Similar to the strategy employed for the detection of CMV viraemia (DNA-emia) attempts were made to use molecular techniques for the early recognition of EBV reactivation. The introduction of real-time polymerase chain reaction (RQ-PCR) several years ago has provided a powerful tool to monitor EBV reactivation in still asymptomatic allo-SCT recipients and to predict increased risk of developing EBV-LPD [2,3].

Discussion

Until recently, clinical management of EBV-LPD was largely restricted to prophylactic strategies, i.e. B-cell depletion of the graft, and therapeutic interventions in the late stages of EBV disease through restoration of T-cellular immunity by means of donor lymphocyte infusion (DLI) or administration of EBV-specific cytotoxic T lymphocytes (CTL). Although effective in some cases, DLI frequently resulted in an unfavourable outcome, whereas clinical grade CTL were only available in few specialized centres.

Recently, evidence has been provided that EBV-DNA load guided preemptive treatment with B cell depleting CD20 monoclonal antibodies (Rituximab®) is effective in preventing EBV-LPD in allo-SCT recipients at high risk [4].

Although effective in preventing EBV-LPD, preemptive treatment based on EBV-DNA load as a single parameter definitely results in unnecessary treatment in a significant number of patients. Since EBV-LPD only occurs in the absence of adequate T cell immunity, we and others retrospectively analysed (EBV-specific) T cell reconstitution during EBV reactivation in paediatric allo-SCT recipients who had received preemptive treatment with CD20 antibodies (Rituximab®) [5,6]. Rapid reconstitution of $CD4^+$ and $CD8^+$ T cells and particularly EBV-specific $CD8^+$ T cells was documented in a significant number of EBV reactivation episodes, suggesting that EBV reactivation might have been controlled without additional help of Rituximab. We obtained support for this hypothesis based on the outcome

in a prospectively monitored cohort of SCT recipients with EBV reactivation [6].

Conclusions

Based on the aforementioned findings we propose that simultaneous and on-line analysis of both EBV-DNA load and T cell recovery will improve the identification of patients at high risk for EBV-LPD. These patients will probably benefit most from preemptive interventions, especially treatment with Rituximab. These findings can probably be extrapolated to other viral reactivations (esp CMV and AdV) that occur during the period of immune reconstitution postSCT.

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