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Long-term follow-up of pediatric patients with EBV-related post-transplant lymphoproliferative disorder

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Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a rare life-threatening complication developing after transplantation, which is caused by suppression of T-cell function [1–4]. PTLD after allogeneic hematopoietic stem cell transplantation (allo-HCT) is usually caused by Epstein-Bárr virus (EBV). Given recent progress in diagnostics and therapy [5, 6], survival from EBV-PTLD has improved from 15% [1] to almost 70% [7]. Nonetheless, little is still known regarding the long-term follow-up of patients treated for EBV-PTLD in the early period after allo-HCT.

We previously reported early outcomes of PTLD patients transplanted in our center between 2007 and 2011 [8]. We hypothesized that after the completion of treatment for PTLD, it has no further impact on overall long-term survival. To establish the truth of this, we performed a long-term follow-up analysis of a group of patients with EBV-PTLD in a single-center pediatric transplant center experience.

Material and methods

Design of study

The following inclusion criteria were implemented for the study: a biopsy-proven or probable EBV-PTLD diagnosis and the use of rituximab in treatment either as single therapy or administered together with other therapeutic approaches as combination therapy. We retrospectively analyzed 12 patients (Table I) with EBV-PTLD after allo-HCT, who were transplanted between 2007 and 2011, whose early outcomes of therapy for PTLD have been presented previously [8]. Our study was approved by the Bioethical Committee of *Collegium Medicum*, Nicolaus Copernicus University, Bydgoszcz, Poland.

Treatment

First line tretament for EBV-PTLD was rituximab, administered at a weekly dose of 375 mg/m^2 intravenously. Reduction of immunosuppression was done whenever possible. Second line therapy was scheduled as chemotherapy in cases of a partial response, stable or progressive disease. Other therapies such as surgery or antiviral agents (mainly cidofovir) were not used in our patients, as recommended by the ECIL [5, 6].

Definitions

Commonly used definitions, specified under Sixth European Conference on Infections in Leukemia (ECIL-6), were used [6]. Proven PTLD was diagnosed when a biopsy or other invasive procedure was performed and EBV was detected in

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Table I. Clinical data of patients

Patient	Age (y)	Diagnosis	Donor, HLA match	Relapse	Survival	Cause of death
1	15.7	AML	UD; 8/10	No	No (0.1y)	PTLD, multiorgan failure
2	19.6	HL	UD; 10/10	No	No (1.1y)	Pneumonia, GvHD
3	19.3	AML	UD; 9/10	No	No (0.3y)	GvHD, CMV, PTLD
4	7.8	ALL	UD; 10/10	No	Yes (11.5y)	
5	6.2	AML	UD; 10/10	No	Yes (11.4y)	
6	4.6	ALL	UD; 9/10	Yes (2.9y)	Yes (10.6y)	
7	16.7	SAA	MSD; 10/10	No	Yes (10.5y)	
8	19.1	ES	UD; 10/10	Yes (0.4y)	No (0.5y)	Relapse, progression
9	18.2	ALL	UD; 9/10	No	No (0.6y)	Septic shock, poor graft function
10	2.4	ALL	UD; 9/10	Yes (0.1y)	No (0.3y)	Relapse, progression
11	11.4	ALL	UD; 10/10	No	No (0.1y)	PTLD, multiorgan failure
12	5.3	AML	UD; 10/10	Yes (1.6y)	No (2.7y)	Relapse, progression

HLA — human leukocyte antigen; AML — acute myeloid leukemia; UD — unrelated donor; PTLD — post-transplant lymphoproliferative disorder; HL — Hodgkin lymphoma; GvHD — graft-versus-host disease; CMV — cytomegalovirus; ALL — acute lymphoblastic leukemia; SAA — severe aplastic anemia; MSD — matched sibling donor; y — years; ES — Ewing sarcoma

a specimen obtained with a test with appropriate sensitivity and specificity, together with symptoms and signs from the affected organ [6]. Probable PTLD was defined when a biopsy was not performed, and when clinically presenting as significant lymphoadenopathy or other endorgan disease accompanied by a high EBV-DNA blood load, and in the absence of other etiological factors or established diseases [6]. Response to treatment was assessed at clinical level, classified as complete remission, partial response, stable, or progressive disease, according to the standard definitions [9].

Statistical analysis

The probabilities of relapse incidence, relapse-free survival, and overall survival were determined using the Kaplan-Meier method. The time from the date of PTLD diagnosis to the date of death due to PTLD, or to the date of death due to other causes, or to the date of the last follow-up, was considered.

Results

Demographics

Patients were transplanted due to acute leukemia (n =9), relapsed/refractory Hodgkin lymphoma, Ewing sarcoma (ES), or severe aplastic anemia. The median age at transplant was 11.4 years (range: 2.4–19). PTLD developed at a median of two months after HCT (range: 0.7–3.5). PTLD was proven by biopsy in four cases; the remaining eight cases were considered to be probable PTLD. In 11/12 cases, transplant was performed from an unrelated donor (six matched, five mismatched). In 11/12 cases, peripheral blood was the source of cells. All patients had lymph node presentation, and seven also had extranodal involvement.

Long-term survival after PTLD

After treatment with a median of four doses (range 2–9) of rituximab, 9/12 patients reached complete remission, while 3/12 died due to progression of PTLD (rapid progression in two patients, slow progression with concomitant chronic GvHD and refractory CMV infection in one). The 100-day survival from PTLD was 0.75, as determined using the Kaplan-Meier method.

In 4/9 patients with remission of PTLD, a relapse of primary disease occurred [two acute lymphoblastic leukemia (ALL), one acute myeloid leukemia (AML), and one ES], after a median of 1.1 years (range: 0.2–2.9). The 3-year relapse-free survival for patients surviving PTLD was 0.56, and the relapse incidence was 0.44.

In three cases, relapse/progression was the cause of death after 0.2–1.0 years. In the patient with AML, a second allo-HCT was performed, followed by a second EBV--PTLD, treated successfully with rituximab. However, another AML relapse occurred and the patient eventually died. Two other patients died due to other complications: one pneumonia with GvHD, and one septic shock with myelosuppression. Finally, 4/12 patients are still alive at 10.5–11.5 years (median 11.0) after allo-HCT, with overall survival of 0.25. The long-term overall survival of patients cured of PTLD was 0.44.

Long-term complications

Of the four long-term survivors, all four suffered from prolonged hypogammaglobulinemia: in three cases this was diagnosed as secondary disease with immunoglobulin supplementation for 2–4 years. Primary hypogammaglobulinemia was diagnosed in one child, who has been on replacement therapy for more than 10 years.

Two of the four surviving patients have long-term endocrinological complications: a 15-year-old boy with hypothyreoidism, and a 17-year-old girl with hypogonadotropic hypogonadism. Autoimmune background of hypothyreoidism was excluded. Both patients are on replacement therapy, with L-thyroxin and with estradiol with lutein, respectively. One patient developed hypertension.

Discussion

In this study, we analyzed the long-term follow-up of a group of patients who were treated for EBV-PTLD after allo-HCT in a single pediatric experience. The short-term survival from PTLD was very good, reaching 75% after completion of rituximab-based therapy. Nevertheless, the main finding of our study was a relatively high relapse incidence and decreased long-term overall survival.

There are several explanations for these results. Firstly, theoretically the treatment of EBV-PTLD could contribute to a relapse of primary disease. We are not in favor of this explanation, which has been outlined in the literature [10]. Kinch et al. [10], in a large cohort study, showed that overall survival of patients with clinically significant EBV-DNA-emia at 5 years was 52% for rituximab-treated patients, which was not inferior to all other patients post-transplant. They concluded that rituximab-based treatment for patients with EBV-DNA-emia did not negatively affect their long-term survival. This finding additionally supports the strategy of monitoring EBV and the use of preemptive therapy in high-risk patients against the development of PTLD. Secondly, we are dealing with aggressive forms of primary disease, both in patients with acute leukemia, and with refractory ES, who had already poorly responded to previous autologous hematopoietic stem cell transplantation (auto-HCT). The third explanation is a development of this concept, i.e. that it may be related to a high predisposition of some patients to malignant transformation. Since PTLD, by definition, should be regarded as a malignancy developing after HCT, this explanation might be the most plausible one.

Another finding of our study is long-term hypogammaglobulinemia, prolonged for a period of at least two years in every patient. This complication may be a clear consequence of therapy with rituximab, which depleted CD20-positive lymphocytes B, thus compromising the production of immunoglobulins. Nevertheless, in one patient we diagnosed primary hypogammaglobulinemia, as there was no spontaneous recovery in B-cell function in this patient during 10 years of follow-up.

In two survivors, we found hormonal dysfunction of thyroid function or sex hormones. Both deficits should, however, be regarded as late complications of high-dose chemotherapy and transplantation, rather than of rituximab-based treatment of PTLD [11].

Apart from PTLD, Epstein-Bárr virus contributes to several diseases after HCT including hemophagocytic lymphohistiocytosis and chronic fatigue, and it increases the risk of several malignancies and the development of graft-versus-host disease [6, 12].

The limitation of our study is the clearly small group of patients. We wanted, however, to point out the complicated correlations between various factors contributing to the final outcomes of transplant therapy and treatment of PTLD.

Summary

We found a relatively high-rate of relapse of primary disease in pediatric patients treated for EBV-related post-transplant lymphoproliferative disorder after allogeneic hematopoietic cell transplantation. This finding is probably more related to the aggressiveness of malignancies in this selected group of patients, rather than to rituximab-based therapy applied for PTLD.

Authors' contributions

Design of the study: JS. Provision of clinical data: PG, MS, KJ, KC, RD, MRP, JK. Interpretation of data: JS, PG, MS, DR. Methdological analysis: JS, DR. Genetic analysis: TG. Writing manuscript: PG, JS, MS. Final approval: all authors.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to biomedical journals.

References

1. Curtis RE, Travis LB, Rowlings PA, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. Blood. 1999; 94(7): 2208–2216, indexed in Pubmed: 10498590.
2. Styczyński J. Infectious complications in children and adults with hematological malignancies. Acta Haematol Pol. 2019; 50(3): 167–173, doi: 10.2478/ahp-2019-0027.
3. Styczyński J. ABC of viral infections in hematology: focus on herpesviruses. Acta Haematol Pol. 2019; 50(3): 159–166, doi: 10.2478/ahp-2019-0026.
4. Styczyński J. Limfadenopatia u dzieci i dorosłych: zasady postępowania diagnostycznego. Acta Haematol Pol. 2019; 50(3): 98–102, doi: 10.2478/ahp-2019-0016.

5. Styczynski J, Reusser P, Einsele H, et al. Second European Conference on Infections in Leukemia. Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. Bone Marrow Transplant. 2009; 43(10): 757–770, doi: 10.1038/bmt.2008.386, indexed in Pubmed: 19043458.
6. Styczynski J, van der Velden W, Fox CP, et al. Sixth European Conference on Infections in Leukemia, a joint venture of the Infectious Diseases Working Party of the European Society of Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN). Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. Haematologica. 2016; 101(7): 803–811, doi: 10.3324/haematol.2016.144428, indexed in Pubmed: 27365460.
7. Styczynski J, Gil L, Tridello G, et al. Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Response to rituximab-based therapy and risk factor analysis in Epstein Barr virus-related lymphoproliferative disorder after hematopoietic stem cell transplant in children and adults: a study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Clin Infect Dis. 2013; 57(6): 794–802, doi: 10.1093/cid/cit391, indexed in Pubmed: 23771985.
8. Styczyński J, Kałwak K, Czyżewski K, et al. Results of therapy with anti-CD20 antibodies in EBV-related post-transplant lymphoproliferative disorder. Post Nauk Med. 2014; 27(4): 261–264.
9. Cheson BD, Pfistner B, Juweid ME, et al. International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25(5): 579–586, doi: 10.1200/JCO.2006.09.2403, indexed in Pubmed: 17242396.
10. Kinch A, Hallböök H, Arvidson J, et al. Long-term outcome of Epstein-Barr virus DNAemia and PTLD with the use of preemptive rituximab following allogeneic HSCT. Leuk Lymphoma. 2018; 59(5): 1172–1179, doi: 10.1080/10428194.2017.1365860, indexed in Pubmed: 28831836.
11. Salooja N, Shoham Z, Dalle JH. Endocrine disorders, fertility and sexual health. In: Carreras E, Dufour C, Mohty M, Kroger N. ed. The EBMT Handbook: hematopoietic stem cell transplantation and cellular therapies. Springer, Cham 2019: 421–427.
12. Styczynski J, Tridello G, Gil L, et al. Prognostic impact of Epstein-Barr virus serostatus in patients with nonmalignant hematological disorders undergoing allogeneic hematopoietic cell transplantation: the study of Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation. Acta Haematol Pol. 2020; 51(2): 73–80, doi: 10.2478/ahp-2020-0015.