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ORIGINAL RESEARCH ARTICLE

Transborder program of allogeneic hematopoietic cell transplantations from unrelated donors for Ukrainian children in Bydgoszcz 2015–2020

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Abstract

Introduction: The aim of this study was the analysis of the organizational aspects, treatments and outcomes of the program of allogeneic hematopoietic stem cell transplantations (HCT) from unrelated donors for children from Ukraine in the Transplant Center in Bydgoszcz, Poland over the period 2015–2020.

Material and methods: Patients from Ukraine were referred via email by parents or by the Tabletochki Charity Foundation based in Kyiv directly to transplant physicians or to the Medical Office of Jurasz University Hospital 1 in Bydgoszcz.

Results: Overall, 28 allo-matched unrelated donor-HCTs in 22 patients were performed. Children were diagnosed for malignant (n = 19) or non-malignant (n = 3) diseases. Most of the children were in advanced stages of the disease. The cumulative probabilities of hematological engraftment measured by neutrophil and platelet recovery were 90.6% and 77.3%, respectively. The cumulative incidence of acute graft-versus-host disease ≥2° and extensive chronic graft-versus-host disease were 40.9% and 27.7%, respectively. Overall, 11/19 patients with malignant diseases and 1/3 with non-malignant diseases were alive at the end of a median follow-up of 1.5 (range 0.1–6.5) years. Overall survival (OS) for all patients was 0.51 ± 0.11. Patients with malignancies at transplant standard risk had OS = 0.83 ± 0.15,

while those with transplant high-risk had OS = 0.34 ± 0.15 (p = 0.025). A total of 10/22 children died. The treatment-related mortality rate was 6/22 (27.3%). The overall relapse rate among children with malignancies was 4/19 (21%).

Conclusions: The program of transborder transplants for children from Ukraine was an important factor in international co-operation contributing to the establishment of a program of transplants from unrelated donors for children in Ukraine. The outcome was positive for more than half of the children referred to the program.

Key words: hematopoietic cell transplantation, unrelated donors, transborder program, children

Introduction

Okhmatdyt (the National Children's Specialized Hospital) in Kyiv, the biggest children's hospital in Ukraine, was the first Ukrainian hospital to perform matched-family donor allogeneic hematopoietic stem cell transplantations (allo-HCT) in children [1]. A program of allo-HCT from unrelated donors in children in Ukraine had started in this hospital in early 2020, just before the coronavirus disease 2019 (COVID-19) pandemic, and two years before the Russian invasion of Ukraine.

The first allo-HCT from an unrelated donor in Ukraine was preceded by a series of training sessions and conferences, including the participation of Polish representatives in a Polish-Ukrainian conference in 2019 in Kyiv, and a subsequent Polish-Ukrainian on-line conference in 2020, followed by several on-line international meetings with the same lecturers.

This activity was preceded by the medical needs of Ukrainian children who required transplants due to malignant and non-malignant diseases, and who lacked family-matched donors. In 2015, the first requests from Ukrainian families came to the Department of Pediatric Hematology and Oncology at Jurasz University Hospital in Bydgoszcz.

The aim of this study was the analysis of the organizational aspects, treatments and outcomes of the program of allo-HCT from unrelated donors for children from Ukraine in the Transplant Center in Bydgoszcz over the period 2015–2020.

Material and methods

Design

All consecutive children and adolescents (aged <18 years) referred from Ukraine to the Department of Pediatric Hematology and Oncology, Jurasz University Hospital 1, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Bydgoszcz, Poland for allo-HCT from an unrelated donor over the period 2015–2020 inclusive were included in the analysis.

Patient referrals

Transplants were made mainly at patients' request, either personally or made via the Tabletochki Charity Foundation (Kyiv, Ukraine) in co-operation with the Medical Office at Jurasz University Hospital 1. Organizational work-up was prepared by the Medical Office. Overall, more than 40 requests were made, but after a formal exchange of information, some of these were withdrawn. In the next step, a formal arrangement was signed between the Hospital and the parents of the patient. Payment was initially finalized after the transplantation was complete, but after a few transplants, formal payment had to be done prior to treatment. Payment came either from the Ministry of Health of Ukraine, or from the Tabletochki Charity Foundation or other Foundations. The Ukrainian Consulate was active in the organization of transplants in a few patients.

Patient qualification

Patients were initially qualified for transplantation by two physicians (JS/RD), and finally by the Department's Transplant Council.

End of program

Two factors contributed to the ending of this program, namely the COVID-19 pandemic announced in March 2020, and the beginning of the program of HCT from unrelated donors in Okhmatdyt, Kyiv. The last patient from Ukraine in this program was admitted to our hospital in March 2020, with the pandemic having already begun. This was possible due to the help of the Polish Ministry of Health, the Border Service and local sanitary-epidemiological services.

Transplant procedures

Patients underwent allogeneic HCT as described elsewhere [2, 3]. All patients received *in vivo* T-cell depletion with rabbit anti-thymocyte globulin (ATG); the total dose was 8 mg/kg

administered over three days. Graft-versus-host disease (GvHD) prophylaxis was performed with the use of cyclosporine ± methotrexate.

Stage of malignant disease

Patients in relapse, secondary malignancy, induction failure, refractory disease or at third or subsequent remission were classified as high risk transplantation. Patients with malignant diseases who did not fulfill these criteria (CR <2) were considered to be standard-risk patients [4].

Prophylaxis of infections

Standard infectious prophylaxis, including environmental prophylaxis, was used according to commonly accepted strategies [5]. Antibacterial prophylaxis included oral phenoxypenicillin, cefuroxime, amoxicillin or ciprofloxacin up to neutrophil recovery and afterwards until the cessation of immunosuppressive therapy. Fluconazole was used for antifungal prophylaxis during the neutropenic phase and fluconazole, posaconazole or voriconazole was given afterwards during immunosuppressive treatment or in case of secondary prophylaxis [6]. Acyclovir was administered for prophylaxis against herpes simplex virus/voricella zoster virus (HSV/VZV) infection until at least one year after transplant [7]. All patients received prophylaxis of post-transplant lymphoproliferative disorders (PTLD) on day +5 with rituximab at a single dose of 200 mg/m^2 [8]. Weekly screening for cytomegalovirus (CMV) and Epstein-Bárr virus (EBV) DNA-emia was done, and preemptive treatment was applied in cases of virus reactivation [5, 9]. Prevention of infection with *pneumocystis jiroveci* included cotrimoxazole until the end of immunosuppressive treatment. Immunoglobulin preparations were administered if immunoglobulin G (IgG) concentration fell below 400 mg/dL.

Definitions

Neutrophil recovery was defined as an absolute neutrophil count ≥0.5 G/L for three consecutive days. Platelet recovery was defined as ≥20 G/L without platelet transfusion for seven days. Acute GvHD (aGvHD) was evaluated in accordance with standard criteria. Chronic GvHD (cGVHD) was determined in patients surviving for ≥100 days after allo-HCT and was classified as either limited or extensive type.

Statistical analysis

Overall survival (OS) was the primary end-point. OS was defined as the time from transplantation to last follow-up or death. The OS and mean survival [with 95% (confidence interval) CI] were calculated using the Kaplan-Meier method and compared using the log-rank test. The analysis was performed with the use of statistical package SPSS 28.0 (IBM, Armonk, NY, USA).

Ethical considerations

All investigations and treatments analyzed in this paper were established clinical practices and were carried out according to accepted clinical practice and in compliance with the medical principles of the Declaration of Helsinki. Informed consent was obtained from all parents and patients (if applicable) prior to treatment. In this retrospective analysis of common clinical practice, formal ethical approval was not required.

Results

Demographics

Between 2015 and 2020 inclusive, 28 allo-matched unrelated donor (MUD)-HCTs in 22 patients were performed. Children originated from various regions of Ukraine (Figure 1). Detailed medical characteristics of patients are set out in Table I. There were 16 boys and six girls, median age 7.6 years. Median Lansky/Karnofsky performance score was 100, although two patients had a score ≤80. Children were diagnosed for malignant (n = 19) or non-malignant (n = 3) diseases. Most of the children were in advanced stages of the disease i.e. were considered transplant high-risk. All patients were CMV-seropositive and 21/22 were EBV-seropositive. Most of the patients were heavily pretreated, after numerous infections including invasive fungal disease, and often colonized with resistant bacteria. Three patients had secondary or therapy-related malignancy. The reason for subsequent transplant was primary graft failure (n = 3), secondary graft failure (n = 1), and relapse (n = 1).

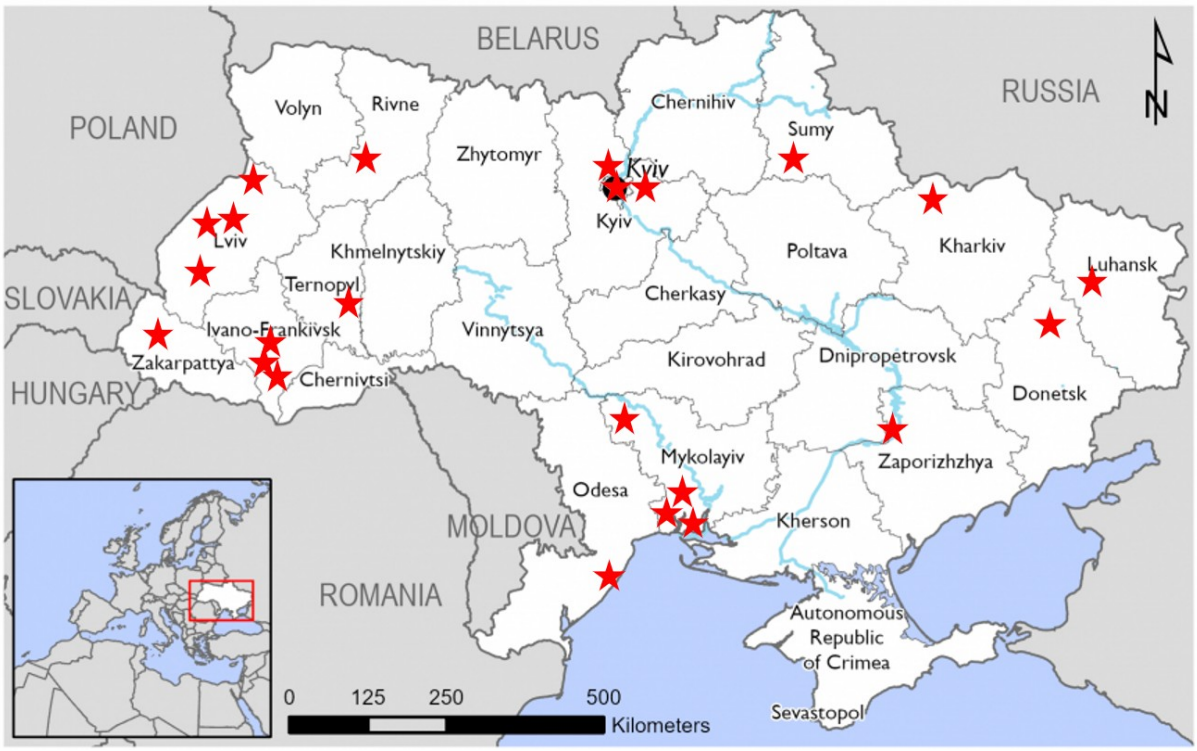


Figure 1. Origin of patients (Ukrainian map: https://fews.net/); each star indicates one patient

Table I. Patient characteristics

Characteristics	**Number [%]**
Sex (male:female)	16 (72.3%):6 (27.7%)
Age (median, range) [years]	7.6 (1.0–17.9)
Lansky/Karnofsky score (median, range)	100 (50–100)
Malignant:non-malignant diseases	19 (86.4%):3 (13.6%)
Diagnosis (malignant)	AML/ABL (n = 10); ALL (n = 6); MDS (n = 3)
Diagnosis (non-malignant)	SAA (n = 1), BDA (n = 1), NBS (n = 1)
Stage of malignant disease	Standard-risk (n = 8); high-risk (n = 11)
Year of transplant	2015 (n = 1); 2016 (n = 6), 2017 (n = 6), 2018 (n = 5), 2019 (n = 3), 2020 (n = 1)
Source of cells	PB (n = 17), BM (n = 5)
CMV serostatus	Positive (n = 22)
EBV serostatus	Positive (n = 21)
Myeloablative conditioning	N = 20 (19/19 malignant; 1/3 non-malignant)
ATG use	N = 22
CD34 cell dose (median, range) [x10^6/kg]	11.1 (4.0–16.2)
Additional transplants	Two (n = 4), three (n = 1)

AML — acute myeloid leukemia; ALL — acute lymphoblastic leukemia; MDS — myelodysplastic syndrome; SAA — severe aplastic anemia; BDA — Blackfan-Diamond anemia; NBS — Nijmegen Breakage Syndrome; PB — peripheral blood stem cells; BM —

bone marrow; CMV — cytomegalovirus; EBV — Epstein-Bárr virus; ATG — anti-thymocyte globulin

Engraftment

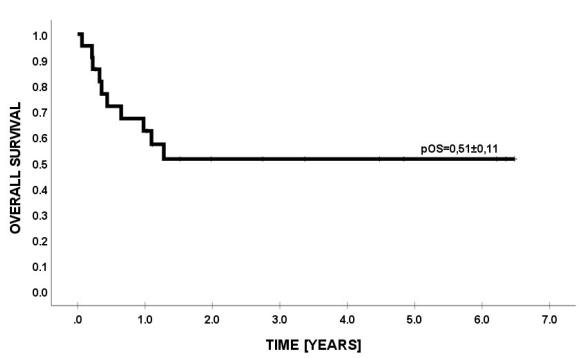
The cumulative probabilities of hematological engraftment measured by neutrophil and platelet recovery were 90.6% and 77.3%, respectively. The median time to granulocyte recovery [absolute neutrophil count (ANC) >500] was 19 days (range 11–30), and the median time to platelet recovery (platelet count >20 G/L) was 16 days (range 11–65).

Graft-versus-host disease

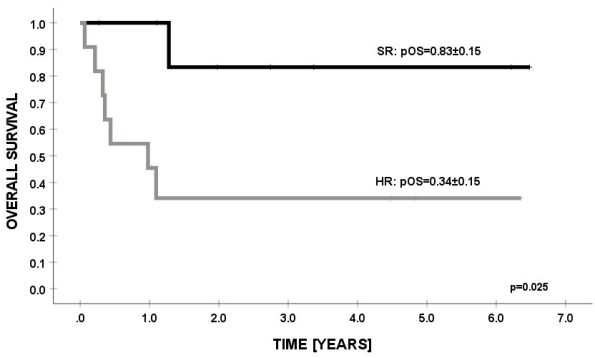
The cumulative incidence of aGvHD ≥2° and extensive cGvHD were 40.9% and 27.7%, respectively: nine patients had aGvHD ≥2°, and 5/18 evaluable patients were diagnosed as having extensive cGvHD.

Outcomes

Overall, 11/19 patients with malignant diseases and 1/3 with non-malignant diseases were alive at the end of the median follow-up of 1.5 (range 0.1–6.5) years. Overall survival for all patients was 0.51 ± 0.11 (Figure 2A). For patients with malignant diseases [acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS)], the OS was 0.54 ± 0.12. Patients with malignancies at transplant standard risk had OS = 0.83 ± 0.15, while those with transplant high-risk (advanced phase) had OS = 0.34 ± 0.15 (p = 0.025) (Figure 2B).



A



B

Figure 2. Probability of overall survival of patients undergoing transplants: **A.** For all patients; **B.** For patients with malignancies stratified by transplant risk: SR — standard risk; HR — high risk

Mortality

A total of 10/22 children died, including relapses followed by infectious complications and multiorgan failure (n = 4), primary graft failure (n = 3), and infectious complications with secondary graft failure (n = 3). The treatment-related mortality (TRM) rate was 6/22 (27.3%). Overall relapse rate among children with malignancies was 4/19 (21%).

Discussion

The program of transborder transplants from unrelated donors for Ukrainian patients was developed to meet the needs of parents seeking medical help for their children. Immediately, cooperation between patients and our hospital was organized by the Tabletoczki Charity Foundation based in Kyiv. This model of cooperation was very efficient, especially because of the highly motivated team from the Tabletoczki Charity Foundation and very good communication between these three, and eventually four, partners. The fourth partner was the Ministry of Health of Ukraine, as this program was financially supported initially by non-governmental organizations, and then by the Ministry of Health of Ukraine. Importantly, the Ukrainian government immediately invested in the new building of the Okhmatdyt hospital, with a large section for hematopoietic cell transplants. In the meantime, a transplant program was developed starting from matched family donors, with swift preparation to transplants from unrelated donors, which obviously always requires international co-operation. Polish physicians also participated in this educational program for pediatric transplants in Ukraine.

The value of our program for Ukrainian children was clear to all partners. It was beneficial for children from Ukraine and their parents, as it gave hope of a cure. This was especially important, as the majority of patients were heavily pretreated, after several lines of chemotherapy and after many complications, including severe infections. The program was beneficial for the Ukrainian government, as it increased the understanding of the Ministry of Health of Ukraine regarding the unmet needs of patients. Okhmatdyt hospital also benefitted, as it accelerated preparation, education, meetings, organizational aspects, and international cooperation [1]. Finally, our own transplant center benefitted, as we were able to help more

children. The outcomes varied, and were not as good as for Polish children [2], because there was a much higher proportion of Ukrainian patients at transplant high risk for a poor outcome qualified for treatment.

The beginning of the program was very difficult. Transborder communication with a non-Schengen country was a real challenge for the Department, and an even more difficult task for the administration of our hospital. Importantly, organizational difficulties in the hospital were finally overcome with the high motivation of the Director of the hospital. We also hosted the Ukrainian Consul, whose personal visit gave a very positive feedback about this international co-operation, and generated great interest from Ukrainian media. This international co-operation was developed much earlier than the war that began with the Russian invasion in February 2022, and so as a transplant center, we were open to help at this time [10].

On the other hand, many Ukrainian families live in Bydgoszcz. There were direct flights from Bydgoszcz to Kyiv, and the region is promoted widely within Ukraine. The long-term co-operation of Ukrainian families in Poland has impacted the lives of patient families: some of them have become Polish inhabitants, while others went back to Ukraine.

The limitation of this study is the nature of the process. This should be more regarded as a social process of international aid. Patient recruitment was based on compassionate-use principles: highly advanced diseases, relatively long process of administrative procedures, some patients/families giving up or not managing to be on time in Poland. The outcomes for these patients were variable due to highly advanced diseases and numerous complications.

But it is most important to state that this program was successful for more than half of the patients, that some patients had repeated HCTs, and that over half of them were eventually cured.

The contribution of the hospital was very significant. The hospital was not able to cover any additional costs of treatment in cases of prolonged therapy of cumulative complications. The financial benefit for the hospital was marginal, with additional costs being covered by the hospital from the initially obtained benefit. Some additional treatments were covered by parents, and some by Polish non-governmental organizations.

In summary, the program of transborder transplants for children from Ukraine was an important factor in international co-operation contributing to the establishment of a program of transplants from unrelated donors for children in Ukraine. The outcome was positive for more than half of the children referred to this transborder transplant program.

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Authors' contributions

JS — design of study, analysis of data, writing. RD, KC, MR-P — collection of data, critical revision of paper. All authors — final approval

Conflict of interest

Nothing to disclose.

Financial support

No financial support.

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.

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