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ORIGINAL RESEARCH ARTICLE

International cooperation to secure access of patients in Ukraine to cellular therapies in conditions of Russian aggression

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Abstract

Introduction: February 2022's wholesale Russian invasion of Ukraine strongly impaired the availability of hematological treatments including hematopoietic cell transplantation (HCT) during the first months. Many activities were initiated by Ukrainian physicians with the support of the international community. Ukrainian refugees received almost unlimited access to treatment in some EU countries, such as Poland.

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Material and methods: Activities of the 'Help for Ukrainian Hematology Patients' (HUP) initiative are described in this article. Information on HCT and cell therapy in refugee patients in Polish transplant centers was collected by questionnaire between 24 February 2022 and 24 February 2023.

Results: Data on 65 patients was available: 22 males and 43 females, with a median age of 35 years. The most frequent diagnoses were Hodgkin's lymphoma (20 patients) and acute lymphoblastic leukemia (17 patients). Allo-HCT was performed in 24 patients, auto-HCT in 36 patients and CAR-T-cells in five patients. Fourteen patients (21.5%) received treatment that was unavailable in Ukraine. The major challenges included social and language issues.

Conclusions: The number of initiatives of Ukrainian physicians and HUP led to a significant increase in the number of HCT procedures in Ukraine after the initial drop-down. The almost unlimited access to healthcare in some EU countries has allowed refugees to get treatment that is unavailable in Ukraine.

Keywords: international cooperation, stem cell treatment, military conflict, refugees

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Introduction

Before the full-scale Russian invasion of Ukraine, eight Ukrainian transplant centers reported a total of 48 allogeneic (six adults and 42 children) and 200 autologous hematopoietic cell transplantations (HCT) (185 adult and 15 pediatric) in 2021, corresponding to respective transplant rates (TR) of 12 and 50 HCT/10,000,000 inhabitants. The TR was similar to that of Latin America and the Asia Pacific region. A lower TR was observed only in the East Mediterranean and African regions [1]. In comparison, TR in Europe for adult and pediatric patients reaches a median of 181 and 258, respectively [2]. Because of the TR gap, centers performing autologous HCT in Ukraine contacted the European Leukemia Net (ELN) and the Worldwide Network for Blood and Marrow Transplantation (WBMT) to help establish modern programs according to JACIE recommendations, as previously reported for other countries (e.g. Paraguay). After a site visit to the facilities, preparations for adult allogeneic HCT started in January 2022. In 2021, only six allogeneic HCTs were performed in adults and 42 in pediatric patients in a country of 40 million inhabitants. Ukrainian patients in need of an allogeneic HCT (allo-HCT) were either transferred to transplant centers in other countries or not transplanted at all. Moreover, CAR-T cell treatment remained unavailable for patients inside the country [3].

Following the Russian invasion in February 2022, physicians, the main scientific organizations in the field, the World Health Organization (WHO), politicians, and diplomats formed the 'Help for Hematological Ukrainian Patients' (HUP) group to coordinate the activity for Ukrainian patients. According to joint decisions by patients and their physician, adult patients in need of hematological treatment were either allocated outside the country with the help of the Lymphoma Coalition and the Polish Society of Hematology and Blood Transfusion (PTHiT) or, whenever possible, in transplant centers with experience in autologous HCT, using modern approaches like supervisory telemedicine and European tumor boards.

In contrast, pediatric patients were mainly transferred to other countries. HUP's activities have allowed the establishment of sustainable transplant programs and increased the number of allogeneic HCTs from six to 45 in adults in 2022. The transplantation program for pediatric patients was resumed after a break: 19 allogeneic HCTs in children were performed in 2022. Thus, at the end of 2022, the drop-off rate in the number of HCTs was only around 10%, from 248 to 223 in total [4, 5]. Several patients were treated outside Ukraine, in European and non-European countries.

Poland was one of the first countries to accept refugees from the first weeks of the war, and this is continuing today. According to data published by the Polish Border Guard, more than 11 million people crossed the Ukrainian-Polish border during the first year of the full-scale Russian invasion [6]. Over 1.5 million Ukrainian refugees have applied for a temporary national protection scheme in Poland and obtained a number confirming their identity (PESEL), assigned to all Polish citizens, as well as to set up a Trusted Profile and later access to an electronic individual patient account (IKP) [7]. The healthcare provisions for Ukrainian refugees are governed by Poland's 'Act on Assistance to Ukrainian Citizens in Connection with the Military Conflict in Ukraine' enacted on 12 March 2022. This legislation ensures nearly equal rights to medical care in Poland for Ukrainian citizens relocated to Poland after 24 February 2022.

In this report, we present the results of the HUP activities, and specifically evaluate the treatment with cellular therapy administered to Ukrainian patients from 24 February 2022 to 24 February 2023, in Poland.

Material and methods

Information on HCT and cell therapy procedures for Ukrainian refugees in Poland was collected by questionnaire from

24 February 2022 to 24 February 2023. Requests for basic data on patients' demographic, family, social, and clinical characteristics, treatment details, and patient needs were sent to the 24 Polish transplant centers.

Results

Ten Polish transplant centers, including one pediatric center and nine adult centers, returned questionnaires with information on 65 patients with hematological malignancies who received HCT or CAR-T cell therapy. The participating centers included: Medical University of Gdansk; Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw; the Institute of Hematology and Transfusion Medicine, Warsaw; Wroclaw Medical University; St. John of Dukla Oncology Center of Lublin; Pomeranian Medical University in Szczecin; Medical University of Lublinn; Provincial Multidisciplinary Center For Oncology And Traumatology M. Copernicus University in Lodz; Medical University of Warsaw; and the Independent Public Clinical Hospital na A. Mielęcki Medical University of Silesia, Katowice.

Patient characteristics are set out in Table I. The patient population mostly comprised younger female patients. The most frequent diagnoses were Hodgkin's lymphoma, acute lymphoblastic leukemia, and non-Hodgkin's lymphoma, covering c.2/3 of all diagnoses. Among the patients treated with allo-HCT, two of them received grafts from related donors (MRD), five from unrelated donors (MUD), and two from haploidentical related donors (HAPLO). For 15 patients, donor data remains incomplete.

Of 65 patients treated in Poland, 29 came from the occupied territories or zones of active military action, while 36 came from more stable territories. Most (47) of the patients came with family members, while 18 had no family member or other caregiver to support them. Of 50 patients treated with second and further treatment lines, 27 received second-line treatment, while 23 received third-line or subsequent treatment. At least seven patients received more than one treatment line. Importantly, at least 14 patients (21.5%) received treatment unavailable in Ukraine. These treatments included CAR-T cell therapy, antibodies in the relapsed ALL (blinatumomab Blincyto®, inotuzumab ozogamicin Besponsa®), nelarabine, and some supportive care drugs. Treatment with limited availability in Ukraine was offered to 25 patients (38.5%). This included immune check-point inhibitors, allogeneic HCT, nelarabine, and various supportive care drugs, such as antibiotics, antifungals, and letermovir.

The primary challenges during the treatment in Poland included social issues (e.g. accommodation, logistics, nutrition, financial support) and the language barrier. Social support from medical staff and volunteers was provided to 16 patients, and 16 (24.6%) required language assistance. Other notable issues were the need to translate the medical records and deal with incomplete medical documentation.

Table I. Patient characteristics

Patient characteristics	Numbers
Gender: m/f, n	22/43
Pediatric population	3
Adult population	62
Age, median (range), years	35 (4–66)
Diagnosis (n):	
Hodgkin's lymphoma	20
Acute lymphoblastic leukemia	17
Non-Hodgkin's lymphoma	10
Acute myeloid leukemia	7
Multiple myeloma	6
Severe aplastic anemia	3
Myelodysplastic syndrome	1
Histiocytosis	1
Type of treatment (n):	
Allogeneic stem cell transplantation	24
Autologous stem cell transplantation	36
CAR-T-cells	5
Status of disease at first admission (n)	
Newly diagnosed	15 (5 diagnosed in Poland)
Disease progression	37
Continued treatment line started in Ukraine	13

The median treatment time in Poland was 10 months (range 2–12). Currently, 48 patients remain in Poland, of whom 26 underwent auto-HCT, 18 received allo-HCT, and four were treated with CAR-T cells. Treatment or active observation in Polish healthcare institutions is ongoing in 35 patients; 13 did not continue follow-up. Six patients treated with allo-HCT returned to Ukraine after the procedure. Eight patients from the whole group died in Poland. Two of them died after auto-HCT due to disease progression, and the other six after allo-HCT due to infectious complications in five cases and thrombotic microangiopathy in one case.

Discussion

Poland faced the largest influx of refugees as a consequence of the Russian invasion of Ukraine of any European country. Around 1.5 million Ukrainian citizens remain in Poland today. By law, Ukrainian refugees have equal rights to medical care in Poland as do Polish citizens. This equality extends to hematological patients, ensuring access to the 'fast-track oncology pathway' model for the diagnosis and treatment of malignancies, including access to special

drug programs, HCT procedures, and cell therapies [8]. An assessment published by British scientists in December 2022 highlighted that the cancer care segment of the Polish healthcare system has the highest capability of handling the anticipated increase in new diagnoses of various cancer types among refugees when compared to neighboring countries of Ukraine. This assessment, based on the number of oncologists, hematologists, radiologists, nurses, available equipment, and infrastructure, graded the capacity of the Polish healthcare system as yellow/green [9]. Nevertheless, the huge increase in the number of patients due to the influx of refugees has been remarkable. Since 24 February 2022, the Polish healthcare system has organized a centralized logistics system and assignment of the arriving patients to hospitals. Until the system was settled, the personal connections and individual activities from the Ukrainian and Polish sides facilitated the relocation and initiation of treatment for refugees in Poland. For example, the PTHiT organized a system of patient referrals to hematological departments around the country and transportation abroad on a case-to-case basis in cooperation with the Ukrainian Hematology Association, the European Hematology Association, and the Lymphoma Coalition. It is vital to underscore that all activities were performed without experience or clear guidelines or a full understanding of what to expect.

The number of new cancer cases (including hematological malignancies) that were anticipated to be diagnosed in Ukrainian refugees in Poland during the year from 24 February 2022, was 3,300, with 52,000 of all cancer cases expected to arrive during this period [8]. Rough calculations based on the transplant rates in the most active transplant countries suggested that at least 90 HCT procedures should be performed among refugees from Ukraine.

According to the accumulated real-life data from almost half of the Polish transplant centers (10/24), 65 HCT and cell therapy procedures were performed on refugee patients from Ukraine during the first year of the war. Robust calculations, factoring in the assumed activity of the remaining centers, suggest that the anticipated number was met. This could be attributed to the easy access to the health system for relocated patients diagnosed with hematological malignancies searching for life-saving treatment possibilities.

Communication problems (language barriers) and social issues were among the most significant challenges for both patients and medical staff. Interpretation was facilitated through the involvement of local medical staff, volunteers, and mobile applications. Some hospitals established internal support systems based on the initiative of Ukrainian and Polish-speaking staff. Medical care reimbursement was not an issue because Ukrainian refugees obtained the same privileges as Polish citizens. However, due to differences in healthcare systems and reimbursement approaches between Poland and Ukraine, in some cases, treatment initiated in Ukraine could not continue. The exact number of patients for whom treatment was delayed, and the duration of such delays, could not be calculated. Incomplete documentation and incorrect translation of the documents were overcome by speedy workups performed at hosting centers. All informed consent forms and educational materials had to be translated into Ukrainian. In contrast to the findings of Puskulluoglu et al., in our experience the social issues regarding logistic, financial, and accommodation problems emerged as the biggest problems [8]. It should be noted that Polish pediatric transplant centers had some experience of treating Ukrainian patients in the prewar period, as opposed to adult centers [10]. The relocation of the patients was performed by the patients themselves or with the help of volunteers from Ukraine or international organizations such as the Lymphoma Coalition, or even with the help of physicians. Medical staff also supported efforts to find accommodation. Notably, some patients lived in the houses of medical staff. For instance, donations from international societies and private individuals enabled support for accommodation in the Polish city of Gdansk. Using a case-by-case approach, an international team of volunteers and patient advocacy organizations searched for clinics, accommodation, and transfer possibilities for patients. Additional challenges directly related to healthcare needs were patients in need who surpassed the line of Polish patients.

Half of the patients in our study were relocated from the zones occupied by Russian military forces, bordering with occupied territories (zones with active military actions) or territories periodically assaulted (e.g. Kyiv). C.70% of the patients traveled with family members and thus had caregivers. Nevertheless, some patients came with children and needed support in caring for them during the hospitalization. Most of the patients stayed in Poland after treatment completion, while those who returned to Ukraine had problems with access to local care due to war conditions. For example, one patient, after allogeneic HCT, strongly motivated to return home, was admitted to the ICU at Homeplace Hospital with signs of severe GvHD and infection a couple of weeks after the discharge to Ukraine, where she could not continue immunosuppressive treatment (cyclosporin) that was locally unavailable. Fortunately, the patient was salvaged by the joint efforts of Ukrainian staff at the Kyiv City Center of Bone Marrow Transplantation and online constant support organized by the European Leukemia Network.

The influx of new patients continued after the first year of war, presenting an ongoing challenge for the Polish healthcare system, constantly adapting to changing conditions. However, according to the calculations, the Polish healthcare system needs an additional 2,370 physicians, 5,016 nurses, and 599 midwives for every million people [7] together with increased funding of the healthcare system generally.

Similarly, Ukraine's healthcare system has adapted to the challenges posed by the war. The substantial increase in HCT procedures performed at the beginning of 2023 corroborates this notion. The statistics presented by the Ukrainian Center for Transplant Coordination show a promising increase in transplant activity in Ukraine. Maintaining this trend might be difficult and require exceptional effort from the Ukrainian healthcare system, but also require constant international help, which is an essential part of the progress in SCT and cell therapy in Ukraine. The successful work of the HUP significantly influences the SCT activity and quality in Ukraine. The HUP has undertaken diverse activities, encompassing educational and scientific initiatives, clinical support, and the supply of drugs and equipment.

The educational and scientific activities include free access to conference materials, the participation of international experts in educational and scientific events in Ukraine, and joint publications. The Ukrainian Association of Bone Marrow Transplantation was founded with HUP support and actively works in the clinical, educational, scientific, and social fields [11].

Clinical activities have included regular consulting provided to Ukrainian HCT centers. HUP members provide daily supervisory telemedicine rounds in the Kyiv City Center of Bone Marrow Transplantation and weekly tumor boards with global experts [coordinated by the European Blood and Marrow Transplantation (EBMT)]. During the weekly HUP meeting, Ukrainian and international members discuss general approaches and key issues. The coordination of treatment in the European centers is discussed during these meetings. Up-to-date diagnostics, including immunophenotype, molecular, and genetic tests, are provided in the Munich Leukemia Laboratory (MLL) without charges for around 20 patients weekly, 582 samples from the beginning of the collaboration. The above-mentioned tests are either not available or only limitedly available in Ukraine. Different organizations financially support the delivery of the samples. The HUP shared standard operating procedures among Ukrainian transplant centers. Assistance in organizing unrelated donor searches allowed 31 transplants to be performed in Ukraine in 2022.

The cytostatic and other classes of anticancer drugs, antimicrobials, and supportive care medications, including defibrotide, were delivered as humanitarian aid to several Ukrainian hematological centers. Freezers set at –86° C for the storage of stem cells/blood samples, thawing water baths, and scales were also received. A few grant proposals are still awaiting responses.

These efforts increased the number of HCT procedures in 2023 to 342, a 40% increase on 2021, including 90 allo-HCT procedures, which is almost double the number in 2021, according to data published by the Center of Transplant Coordination. The Ukrainian Bone Marrow Donor Registry supported the search and transport of stem cells for the 45 unrelated transplantations. Moreover, since 2023, the first five Ukrainian donors from the Registry donated cells for unrelated transplantation for patients inside the country and abroad. Two new centers started transplant programs [12]. Together with HCT procedures performed abroad, this should cover around a quarter of Ukrainian needs. Poland, which has some limitations in terms of access to novel therapies and modern diagnostic tools such as next-generation sequencing, remains one of the European countries providing full health services to Ukrainian refugees.

Conclusions

Ukrainian patients, due to the Russian invasion of their country, have had impaired access to HCT. But the number of HCTs performed in Poland has compensated for the war-induced loss. Nevertheless, per year, the number of HCTs performed in Ukraine and Poland covers less than 15–20% of the expected needs. Ukrainian physicians' courageous and dedicated work, together with treatment abroad and internationally, has opened up new opportunities previously unavailable for patients. Nevertheless, there is still a huge unmet need to improve access to HCT for Ukrainian patients in Europe and back in Ukraine. The increasing number of HCTs in Ukrainian centers underscores the importance of the HUP's activities. This situation calls for the active assistance of all international societies in providing guidelines and training for Ukrainian physicians, hopefully leading to the establishment of more transplant centers, and expanding access to HCT and cell therapy for patients in Ukraine.

Key messages:

- A significant fall in the number of hematopoietic stem cell transplantations (HCT) in Ukraine was observed in the first months after the Russian invasion.
- The courageous and dedicated work of Ukrainian physicians, together with international efforts, increased the number of HCTs up to the end of the first year of the war and opened up new opportunities for Ukrainian patients abroad, e.g. in Poland.
- Nevertheless, the number of HCTs performed in Ukraine and abroad for Ukrainian patients per year still covers only 15–20% of the expected needs.

Article information and declarations

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Authors' contributions
KF was responsible for conceiving idea, designing questionnaire, collecting and analyzing data, interpreting results,

writing manuscript, and updating reference lists. SyK, SeK, EPK, AKL, MM, OK, BB, AF, II, AT, KC, MB, AC, WL, BM, KD, OGI, AW, GWB, GH, YS, OL, and IK were responsible for collecting and analyzing data. ELM collected and analyzed data. She inspired and coordinated process of relocation and treatment of patients in Poland. IH contributed to data collection and analysis. She coordinated process of relocation and treatment of patients in Poland. JMZ contributed to development of present idea and addition of questionnaire. JMZ and DN as senior authors supervised project and inspired colleagues. All authors discussed the results, provided critical feedback, and contributed to the final manuscript.

Conflict of interest

The authors declare they have no known financial or non-financial competing interests as defined by Nature Research, or other interests that might be perceived to influence the interpretation of this article.

Data availability statement

This article's data will be shared upon reasonable request to the corresponding author.

Ethics statement

Authors declare that informed consent for publication was not obtained, as published data does not allow for patient identification.

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