

Evaluation of Leukemia and Solid Tumors in Refugee Children in Turkey: A Tertiary Center Experience

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Abstract

Cancer care is progressively became as a significant worldwide challenge. Wars can cause destructions and delays in cancer diagnosis and treatment of displaced people. Cancer cure rates need to be improved in indefensible populations such as refugees. In this study, we purposed to highlight the clinical peculiarities and outcomes of refugee children with cancer in our hospital. Our purpose was to present our findings and contribute to improve the health care for these children. Seventy one refugee pediatric patients admitted to the oncology and hematology units of our hospital between April 2011 and January 2019 were included in this study. The demographic characteristics of the patients at the initial diagnosis, their countries of origin, living conditions, histopathological diagnoses, treatments, relapse, and mortality data were analyzed retrospectively from the patient files. The median age of patients was 6.5±4.5 years, and the male-to-female ratio was 39/32. While 44 patients (61.9%) presented with complaints and had primary diagnoses in our hospital, the remaining 27 patients (38.1%) were diagnosed in their country and applied to our hospital for treatment. Our mean follow-up period was 18.2±18.8 months (1-90 months). As a result, 44 patients (62%) were alive and 22 (31%) were dead. The survival rate without relapse in the second year was 83.6%. Two and five-year survival rates were 77.5% vs. 58.1% respectively. Compared to Turkish children, lower survival rates were found in refugee children. In addition to cancer-specific factors such as tumor type and stage, some problems such as shelter, communication, adherence to treatment, and difficulties supplying medicine may be responsible for lower survival rates in refugee children. Further studies are needed to improve the survival rates of patients.

Keywords: Refugee children, cancer, survival



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Introduction

Turkey is the country that hosts the most refugees in the world and continues to be home to the world's largest refugee population. Refugees are defined as those who are pushed to part from their houses in consequence of persecution by The United Nations High Commissioner for Refugees. According to the data, in Turkey, approximately 3.6 million Syrians, 172 thousand Afghans, 142 thousand Iraqis, 5,700 Somalis, 39 thousand Iranians, and 11.7 thousand other country refugees are under temporary protection status as of July 2019. In Turkey, there are nearly 1.4 million refugees are under the age of 15 and more than 800,000 are between the ages of 15 and 24.¹ Over 98 percent of refugees in Turkey live in peri-urban, urban, and rustic areas, generally placed in rented houses or relatives' homes, while the remaining live in Temporary Accommodation Centres.

Cancer care is progressively become as significant global challenges, in consequence of financial, global, social, and health inference. Wars and conflicts can conduce great devastation and disruption to patients already being treated for malignancy, and delays in the diagnosis and treatment of these people. Patients with malignancy are undefended to such contingencies that affect the standard of medical care they take, and the medications for the disease treatment.² They usually present in advanced disease and further complications develop in these patients. These patients' outcomes are poor due to poor living conditions and hygiene, along the limited access to care, health education, and facilities available to them. In their asylum countries, they are often unfamiliar with the health-care system, and not enrolled in screening programs.^{3,4}

The Turkish Disaster and Emergency Management Presidency has supported health services, basic daily needs, and regular education institutions, since the beginning of the crisis in 2011.⁵ A Temporary Protection Regulation was passed by The Turkish State to make legal the situation of immigrants, thus achieving free healthcare and medicine including cancer treatment. Primary or secondary care centers refer to the refugees who need to special care tertiary care centers.⁶

To the best of our knowledge, in Turkey, limited number of studies have been reported including refugee children with cancer in the literature.⁷ Therefore we aimed to highlight the number and clinical peculiarities and outcomes of refugee children in tertiary care hospital. Our purpose was to present our findings and could understand the problems to advance the health care for refugee children.

Material and Methods

This study was designed to appreciate the clinical and social characteristics of cancer patients among refugee children. The study group comprised of refugee

children with leukemia or solid tumor who were on treatment between April 2011 to December 2018 in our hospital. Descriptive data consisting of demographics, histopathological diagnosis, the countries of origin, living conditions, previous and current treatments, treatment compliance, relapse or progression status,

outcomes, relapse, and mortality data were retrospectively analyzed from the patient's medical records. All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki. Informed written consent has been taken from parents or guardians before the study (Ethics committee approval: University of Health Sciences Turkey, Ankara City Hospital, approval no: 23.12.2022, E2-22-3020).

Statistical Analysis

Statistical analyses of the study was performed using SPSS 16 statistical programme. Categorical variables were stated as numbers and percentages, and mean \pm standard deviation, minimum-maximum, and median values were used for expressing numerical variables. To compare the differences between groups, the Student t-test was used and Mann-Whitney U test was used for comparisons of median values. As the time from treatment to death, regardless of disease recurrence was defined overall survival. Kaplan-Meier method was applied to estimate survival curves. For the estimation of survival, adjusted hazard ratio and 95% confidence interval were used. $P < 0.05$ was defined as statistically significant.

Results

A total of 71 refugee children who were admitted to our center with a diagnosis of malignancy were included in the study. The median age of our patients was 6.5 ± 4.5 years (11 months-12 years), and the female-to-male ratio was 32/39. The countries of our patients were as follows; 36 of our patients were from Syria (50.7%), 16 were from Iraq (22.5%), 7 were from Afghanistan (9.9%), and 12 were (16.9%) from other countries. Primer diagnoses of the patients were as follows; 12 children with acute lymphoblastic leukemia (ALL) (16.9%), 10 children with brain tumors (14%), 9 children non-Hodgkin lymphoma (12.6%), 8 children with neuroblastoma (11.2%), 5 children with rhabdomyosarcoma (7%), 5 children with retinoblastoma (7%), 4 children with Ewing sarcoma/PNET (5.6%), 3 patients with Langerhans cell histiocytosis (4.2%), 3 patients with acute myeloid leukemia (AML) (4.2%), 3 patients with Wilms tumor (4.2%), 2 patients with Hodgkin lymphoma (2.8%), 2 patients with squamous cell carcinoma (2.8%), 2 patients with osteosarcoma (2.8%), and the other 3 patients with germ cell tumor, hepatoblastoma, nud-midline carcinoma. Tumor and patients' characteristics are summarized in **Table 1**. Communication was achieved using an official translator for patients' families. In total, 45 families (63.3%) had a consanguineous marriage, and 22 (30.9%) were between first cousins. The reason

Highlights

- In refugees cure rates of childhood cancer need to be improved.
- Besides cancer-specific factors such as stage and tumor type, some problems such as shelter, communication, difficulties supplying medicine, and compliance to treatment might have been responsible for lower survival rates in refugee children.

for migration was mostly ongoing war for 50 families (70.4%) and health problems and war for the others. Conditions of shelter revealed that 49 families (69%) were living in rented houses, and 22 families (31%) were living in guesthouses.

Of 71 patients, 44 patients (61.9%) presented with complaints and had a primary diagnosis in our hospital, the remaining 27 patients (38.1%) were diagnosed in their country and applied to our hospital for treatment. Of the 27 patients who were diagnosed in their country, 21 patients (29.6%) had begun treatment in their country but could not be completed due to war or inadequate health care. The diagnoses of 27 patients diagnosed in their country were as follows: 3 patients with a brain tumor, 3 patients with retinoblastoma, 3 patients with ALL, 3 patients with relapsed ALL, 2 patients with rhabdomyosarcoma, 2 patients with Wilms tumor, 2 patients with Ewing sarcoma/PNET, 2 patients with relapsed Hodgkin lymphoma, the others were neuroblastoma, Burkitt lymphoma, Langerhans cell histiocytosis, osteosarcoma, AML, relapsed Wilms tumor, relapsed anaplastic large cell lymphoma (ALCL), relapsed neuroblastoma.

All patients were treated with appropriate chemotherapy protocols for histopathological diagnosis. The patients with ALL received the ALL-BFM 2009 protocol,⁸ and patients with AML were treated with the AML-BFM-2013 protocol.⁹ Patients with neuroblastoma received the

TPOG neuroblastoma 2009 protocol.¹⁰ Patients with non-Hodgkin lymphoma, Burkitt lymphoma, and ALCL received the NHL-BFM protocol.¹¹ Patients with rhabdomyosarcoma received the RMS 2005 protocol.¹² Vincristine, etoposide, and carboplatin (VEC protocol) was used are for patients with retinoblastoma.¹³ Patients with Ewing sarcoma received the Euro-EWING 99 protocol.¹⁴ Patients with Langerhans cell histiocytosis received the LCH-IV protocol.¹⁵ Patients with Wilms tumor received the NTWS-5 protocol.¹⁶

Treatment change was performed in 11 patients (15.5%) who showed progression without responding to primary or relapse treatment. These patient's diagnoses were as follows; 2 patients with Ewing sarcoma, the others were respectively Hodgkin lymphoma, Burkitt lymphoma, neuroblastoma, Wilms tumor, rhabdomyosarcoma, Langerhans cell histiocytosis, nud-midline carcinoma, ALCL, and ALL. Treatment modalities consisted of neoadjuvant and adjuvant chemotherapy, surgical resection, radiotherapy, and bone marrow transplantation. According to their treatment protocol, surgical resection was performed in 30 patients and 6 patients received radiotherapy. Furthermore, bone marrow transplantation was performed in 6 patients (8.5%). Four of these were autologous and two were allogeneic stem cell transplantation. The diagnosis of transplant patients was as follows; 2 patients with neuroblastoma, the remainings were respectively, Ewing sarcoma, ALL, relapsed ALL, and relapsed ALCL. Seven patients (9.9%) relapsed an average of 9±6.1 months after the end of treatment. The median follow-up period was 18.2 months (1-90 months). After a median follow-up 22 (31%) patients died due to primary refractory or relapsed disease. Five patients' latest status is unknown because of the discontinuation of the treatment and follow-up. The survival rate without relapse of our patients in the second year was 83.6% (**Figure 1**). Two and five-year survival rates of the whole group were 77.5% vs 58.1% respectively (**Figure 2**).

Treatment modalities, side effects, and outcomes are shown in **Table 2**. The most common side effect was febrile neutropenia in 21 patients (29.5%). All patients with febrile neutropenia were hospitalized and given antibiotic therapy. The chemotherapy compliance rate

Table 1.
Patient and tumor characteristics

Characteristics	n (%)
Median age, years (range)	6.5±4.5 (11 months-12 years)
Gender	
Male/female	39/32
Countries	
Syria	36 (50.7%)
Iraq	16 (22.5%)
Afghanistan	7 (9.9%)
Others	12 (16.9%)
Diagnosis	
Acute lymphoblastic leukemia	12 (16.9%)
Brain tumors	10 (14.1%)
Non-Hodgkin lymphoma	9 (12.6%)
Neuroblastoma	8 (11.2%)
Rhabdomyosarcoma	5 (7%)
Retinoblastoma	5 (7%)
Ewing sarcoma/PNET	4 (5.7%)
Langerhans cell histiocytosis	3 (4.3%)
Acute myeloid leukemia	3 (4.3%)
Wilms tumor	3 (4.3%)
Hodgkin lymphoma	2 (2.8%)
Squamous cell carcinoma	2 (2.8%)
Osteosarcoma	2 (2.8%)
The others	3 (4.3%)
Sheltering of families	
Rented house	49 (69%)
Guesthouse	22 (31%)

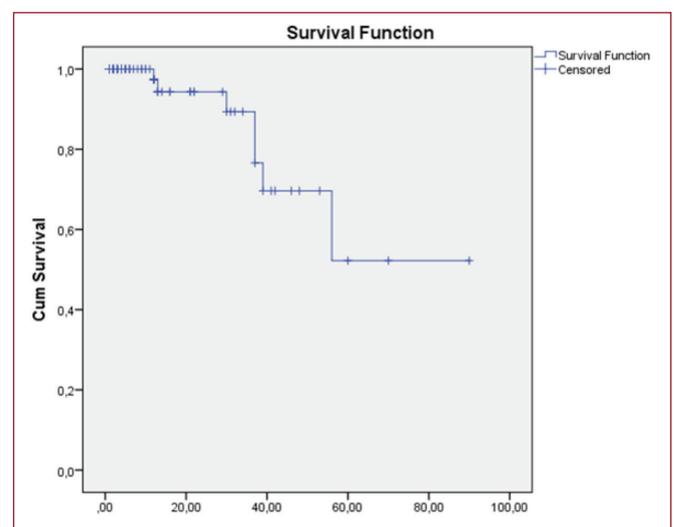


Figure 1. Relapse-free survival rates of our patients.

for patients was 87.3% (n=62). Statistical analysis failed to show a significant relationship between the living site (rented house or guesthouse) and the compliance rate of the patients. Additionally, there was no significant relationship between the living site and the febrile neutropenia episode ($p>0.05$).

Discussion

In this retrospective study, we aimed to investigate the types of cancer and outcomes seen in refugee pediatric patients in our tertiary hospital.

Most of the people were affected by the war in Syria, and most of them came from cities where a war was going on. Actually, they frequently explain their reason for migration was the war. Providentially, they achieved a health institution in Turkey once possible.

Refugee children's cancer treatment is interrupted, or a new cancer is developed while living in host countries. They usually present with advanced disease and

experience further complications. Because of living conditions and poor hygiene, such as limited accession to the health care, and resources available to them, these patients have poor outcomes. In their countries they are not record in screening programs.

Communication difficulties and language differences are another obstacle to be overcome in the treatment for refugee patients. Even though, a translator or telephone translation service were ensured by the Turkish Government, often not enough translators could be found. In case of need health personnel who can speak Arabic was helped.

For inpatients, all of the medication was ensured in the hospital but sometimes for outpatients, medications were a problem, as medications take longer to provide because all prescriptions have to be registered by government agencies.

In our study, the chemotherapy compliance rate was 87.3%, and the compliance rate was to be poor, especially in outpatient settings whom uses oral drugs, for example, patients whom in the maintenance phase of leukemias or lymphomas.

Similarly to developing countries and Turkey, leukemia, lymphoma, and CNS tumors were found to be the most common cancers in our study. Most of the patients (n=44, 61.9%) were diagnosed in Turkey. The patients' chemotherapy compliance rate was not bad, 87.3%, and the most common side effect was febrile neutropenia in 21 patients (29.5%). Although we expected more frequent febrile neutropenia attacks in patients with poor hygienic conditions and staying in the guesthouse, there was no statistically significant difference in febrile neutropenia and complication rates between those staying at home and in the guesthouse.

In Turkey, the 5-year survival rate in children with cancer, including solid tumors and leukemias, was found 69.5%.¹⁷ In another study, Kebudi et al.¹⁸ reported 7-year survival rates of 74% in patients with cancer at specific cancer centers in Turkey. Yağcı-Küpeli and Özkan¹⁹ reported that refugee children had a lower treatment compliance and high frequency of advanced/metastatic disease compared to Turkish children. In our study, the 5-year survival rate of refugee children with cancer was found to be lower than those of Turkish children, that five-year survival rate was 58.1%.

Cancer in refugees causes a major burden on the health systems of the host countries. Patients and their families were confronted with some problems such as hygiene, communication, language barriers, shelter, difficulties in supplying medicine, and compliance with treatment. Advanced or relapsed disease in diagnosis and these socioeconomic problems adversely affect the prognosis and survival of these patients. Therefore, we concluded that there may be significant challenges for cancer patients with early diagnosis. One reason may be the difficulty to reach the free screening program of the Turkish Ministry of Health on the other hand when they have a proven cancer diagnosis, they easily reach health system facilities and get treated with chemotherapy, radiotherapy, and surgical operations.

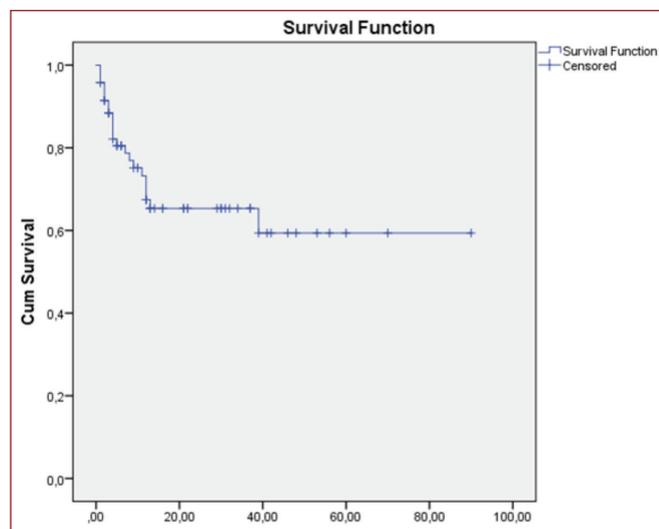


Figure 2. Two and five-year overall survival rates of patients.

Table 2.

Treatment modalities, side effects, and outcomes

	n (%)
Treatment modalities	
Chemotherapy	71 (100%)
Radiotherapy	6 (8.5%)
Surgery	30 (42.2%)
Bone marrow transplantation	6 (8.5%)
Autologous	4 (5.7%)
Allogenic	2 (2.8%)
Side effects	
Febrile neutropenia	21 (29.5%)
Fungal infection	5 (7%)
Paraplegia	1 (1.4%)
Portal hypertension	1 (1.4%)
Dilated cardiomyopathy	1 (1.4%)
Final status	
Deceased	22 (31%)
Alive	44 (62%)
Unknown	5 (7%)

We acknowledge that the current study has several limitations. Retrospective design of the study, and the limited number of patients could not be generalized to the entire refugee children in Turkey. Our median follow-up period was 18.2 months (1-90 months) and it was relatively adequate. Recommendations to increase the prevention, diagnosis, and treatment of cancer in refugee children include improved health systems and screening programs, and innovative financing schemes. Information for refugee patient's families, about how and when to look for medical care should be more appropriate, that this could detect cancers at early stages and would lead to better prognosis and less-costly treatment for these patients.²⁰

Conclusion

Our data showed that cancer survival rates are lower in refugee children, and further prospective studies are needed to determine and improve the socioeconomic problems affecting survival rates in these patients.

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Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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