Unique barriers to care and outcomes of pediatric acute lymphoblastic leukemia treatment in the Gaza Strip

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Abbreviations

95% CI	95% confidence interval
ALL	acute lymphoblastic leukemia
BFM	Berlin-Frankfurt-Muenster
EFS	event-free survival
LMICs	low- and middle-income countries
oPt	occupied Palestinian territory
OS	overall survival
OSH	outside hospital
RPSH	Rantisi Pediatric Subspecialized Hospital
QI	quality improvement
St. Jude	St. Jude Children's Research Hospital

ABSTRACT

Background:

Childhood acute lymphoblastic leukemia (ALL) is the most common pediatric cancer worldwide.[1,2] Although children in high-income countries enjoy survival rates of approximately 90%,[3] children in countries with limited resources suffer from survival rates of less than 35%.[4–7] No published data on pediatric cancer incidence, management, or outcomes in the Gaza Strip are available.

Methods:

A retrospective cohort study was undertaken for pediatric ALL diagnoses admitted to the only pediatric cancer ward in the Gaza Strip between 2010 and 2015. Outcomes included Event-free survival (EFS) and overall survival (OS) calculated by Kaplan–Meier estimates. Events were defined as induction failure, relapse, and death.

Results:

The 3-year EFS estimate was 80% (95% confidence interval [CI], 66%–89%) (Figure 1). The EFS at 1 and 3 years for high-risk ALL was 55% (95% CI, 27%–76%) and 23% (95% CI, 4%–51%), respectively (Figure 1). The 3-year OS was 93% (95% CI, 82%–97%) (Figure 2). The 3-year OS for high-risk ALL was 69% (95% CI, 30%–90%). All 84 (100%) patients required referral to an OSH for definitive ALL diagnoses and induction therapy. Forty-four (52%) patients required at least one additional referral.

Conclusions:

The overall outcomes demonstrated relatively high survival rates at 3 years which may be artificially elevated due to exclusion of adolescents, limited follow up, and deceased patient charts unavailable. Structural determinants of health in Gaza lead to limited diagnostic and treatment capabilities, limited access to advanced medical training, and reliance on out-of-territory transfers for care. These barriers impact the access to comprehensive pediatric care within the Gaza Strip.

1 | INTRODUCTION

Childhood acute lymphoblastic leukemia (ALL) is the most common pediatric cancer worldwide.[1,2] Although children in high-income countries enjoy survival rates of approximately 90%,[3] children in countries with limited resources suffer from survival rates of less than 35%.[4–7] Furthermore, 80% of pediatric patients with ALL reside in low- and middle-income countries (LMICs). Barriers to care in these countries include lack of access to accurate diagnosis, inconsistent resource allocation, complications from drug toxicity, and high abandonment rates. Underlying sociocultural, political, and economic inequity are at the foundation of these barriers.[8–11] Recently, quality improvement (QI) initiatives at oncology centers in LMICs have specifically focused on improving pediatric ALL outcomes because of the high prevalence of disease and the potential for cure with relative low cost of treatment.

The Gaza Strip, located in the occupied Palestinian territory (oPt), is classified as an LMIC.[12] The Pediatric Subspecialty Hospital (PSH) in Gaza City houses Gaza's only dedicated pediatric oncology program. Despite the availability of pediatric oncology care, the children of Gaza face a wide variety of unique barriers to receiving effective oncology treatment. The well-documented economic, social, and conflict-related stressors in Gaza affect all sectors of the health care system in the oPt.[13–15] Currently, no published data on pediatric cancer incidence, management, or outcomes in the Gaza Strip are available. To address this shortcoming, we describe the barriers to care and historical treatment outcomes for pediatric patients with ALL who received care in the Gaza Strip before implementation of recent pediatric oncology QI initiatives.

2 | METHODS

The PSH is a pediatric hospital dedicated to subspecialty care in Gaza City. At the time of the study, the oncology ward had 12 beds, minimal diagnostic resources, frequent chemotherapy shortages, and no local access to subspecialty surgeons or radiation therapy. A retrospective cohort study was undertaken, and we identified 131 potential new pediatric ALL diagnoses admitted to the PSH between 2010 and 2015 through a database review of the International Statistical Classification of Diseases and Related Health Problems (i.e., ICD 9) codes. These were cross-referenced with a written log of new cancer diagnoses maintained by the pediatric oncology group.

A total of 84 charts met the following inclusion criteria: (1) aged less than 12 years at the time of diagnosis, which is the standard age definition for pediatric patients in the oPt, and (2) an initial diagnosis of ALL by morphologic bone marrow evaluation in Gaza and confirmed by flow cytometry at an outside hospital (OSH) due to limited diagnostic techniques in Gaza. The OSHs comprised hospitals located outside of the Gaza Strip. Referral locations and indications for referral were collected. Risk stratification was determined by the international ALL protocols used during the study period: the German Berlin-Franklin-Muenster (BFM) and St. Jude Children's Research Hospital (St. Jude) protocols. Event-free survival (EFS) and overall survival (OS) were calculated by Kaplan–Meier estimates,[16] with standard errors using the Greenwood formula and log–log confidence limits. Events were defined as induction failure, relapse, and death. The start times for the EFS and OS calculations were defined as the date of initial diagnosis from bone marrow findings.

3 | RESULTS

3.1 | Patient Characteristics

We identified 131 charts for analysis, 84 of which met inclusion criteria. Of the 47 charts excluded from our study, 13 could not be located and 34 included diagnoses other than ALL. Of the patients with ALL, 72 (86%) had pre-B cell and 12 (14%) had T-cell immunophenotypes. Patient characteristics are summarized in Table 1. The median age at diagnosis was 3.6 years, and 50 (60%) patients were male. ALL cases were stratified as standard (low) risk in 64 (76%) patients, intermediate risk in 3 (4%), and high risk in 17 (20%). Treatments were administered according to the following protocols: BFM 2002, BFM 2009, or BFM unknown in 64 (76%) patients; St. Jude in 15 (18%) patients; and unknown in 5 (6%) patients.

3.2 | Outcomes

The 3-year EFS for all patients with ALL was 80% (95% confidence interval [CI], 66%–89%) (Figure 1). The EFS at 1 and 3 years for high-risk ALL was 55% (95% CI, 27%–76%) and 23% (95% CI, 4%–51%), respectively (Figure 1). The 3-year OS was 93% (95% CI, 82%–97%) (Figure 2). The 3-year OS for high-risk ALL was 69% (95% CI, 30%–90%). The EFS and OS rates are summarized in Tables 2 and 3.

3.3 | Referrals and Barriers to Care

Each of the 84 patients with ALL receiving treatment at RPSH (100%) required a minimum of one referral to an OSH for definitive ALL diagnosis and induction therapy. Forty-four (52%) patients required at least one additional referral for the following

indications: methotrexate drug level monitoring (*n* = 28), chemotherapy shortages (*n* = 8), treatment for relapsed disease (*n* = 5), induction failure (*n* = 5), . The patients were referred to OSHs in the following countries or territories: Israel (*n* = 36, 43%), West Bank (oPt) (*n* = 43, 51%), Jordan (*n* = 2, 2%), and Egypt (*n* = 3, 4%).

4 | DISCUSSION

The barriers to care in low-resource settings continue to affect the care of pediatric patients with ALL, a disease which is largely curable when access to accurate diagnosis and to relatively inexpensive chemotherapy treatments are available.[8–12] The Palestinian health care system is comprised of a patchwork of health services provided by the MOH, the United Nations Relief and Works Agency (UNWRA), local and international NGO's, and the private sector, and relies on medical referrals to OSH's for advanced care unavailable in the Gaza Strip.[17] Every child with a preliminary diagnosis of ALL required referral to an OSH for definitive diagnosis and induction therapy because of limited diagnostic capabilities, inconsistent access to chemotherapy, lack of supportive intensive care, and limited resources and expertise. Furthermore, more than half of these patients required at least one additional referral due to chronic chemotherapy shortages in the Gaza Central Drug Store.[18] Accessing OSHs is a complicated process requiring coordinated efforts from multiple physicians, international organizations, and security apparatuses. Referrals are frequently delayed and can be denied, as border crossings are subject to frequent and unpredictable closings.[15] Delayed treatment may disproportionately affect critically ill patients and those with high-risk disease, requiring prompt critical care services unavailable in Gaza.

The patient characteristics in Gaza, including sex, median age at diagnosis, and immunophenotype, are similar to those in the United States.[3] The overall outcomes demonstrated relatively high survival rates at 3 years, but data were not available to analyze 5-year survival rates. The relatively high survival rates may be artificially elevated for several reasons. We excluded adolescents, who are typically at a higher risk for poor prognostic cytogenetics,[19] from the study because of the pediatric age cutoff of 12 years in the oPt. In Gaza, children are transferred to adult oncology centers at 12 years of age, which limited our follow-up for patients past this age. Furthermore, the charts of deceased patients are transferred to a central records department, which was inaccessible to us. This limited our ability to account for potential deaths during the study period. When we stratified the outcomes by risk, we found that patients with high-risk ALL had very poor outcomes. The causes of these poor outcomes may be due to biologic disposition, such as a high-risk cytogenetic predisposition. However, the poor outcomes are more likely due to structural determinants of health, such as barriers to care affecting timely access to treatment.

Addressing the barriers to care in pediatric oncology in Gaza is underway. Principles from other successful interventions at limited-resource centers worldwide are being implemented through a unique partnership.[7] In 2012, a non-government organization and the oPt Ministry of Health partnered to launch a QI initiative to improve pediatric oncology care. This QI initiative uses a multitargeted approach, including infrastructure improvement, mitigation of chemotherapy and other resource fluctuations, and implementation of physician and staff education initiatives, to improve pediatric ALL outcomes in Gaza.[20] Consequently, there is a plan to increase the age limit for what are

considered pediatric patients to include patients up to 14 years old because pediatric protocol-based treatment of adolescents with ALL has demonstrated improved outcomes over those treated according to adult protocols.[20] The ultimate goal of the QI initiative is to provide full-spectrum ALL diagnoses and treatments, thereby decreasing or eliminating referrals to OSHs, decreasing treatment delays, and improving the continuity of pediatric oncology care.

In conclusion, pediatric oncology patients and practitioners in the Gaza Strip face structural barriers to all aspects of providing high-quality and timely pediatric cancer treatments. Despite these challenges, a unique QI partnership may provide educational, infrastructural, and material support to address these barriers, ultimately improving the care and outcomes for children with ALL in Gaza.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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None

DATA AVAILABILITY

The data that support the findings of this study are available upon request from the corresponding author.

REFERENCES

1. Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol*. 2010;28:2625-2634.

2. Linabery AM, Ross JA. Trends in childhood cancer incidence in the US (1992–2004). *Cancer.* 2008;112:416-432.

3. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med*. 2015;373:1541-1552.

4. Metzger ML, Howard SC, Fu LC, et al. Outcome of childhood acute lymphoblastic leukaemia in resource-poor countries. *Lancet*. 2003;362:706-708.

5. Howard SC, Pedrosa M, Lins M, et al. Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. *JAMA*. 2004;291:2471–2475.

6. Mostert S, Sitaresmi MN, Gundy CM, Sutaryo, Veerman AJ. Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. *Pediatrics.* 2006;118:e1600-e1606.

7. Howard SC, Marinoni M, Castillo L, et al. Improving outcomes for children with cancer in low income countries in Latin America: a report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO)-Part I. *Pediatr Blood Cancer*. 2007;48:364-369.

8. Bonilla M, Moreno N, Marina N, et al. Acute lymphoblastic leukemia in a developing country: preliminary results of a nonrandomized clinical trial in El Salvador. J Pediatr Hematol Oncol. 2000;22:495-501.

9. von Stackelberg A, Karatchunsky A, Kudrjashova J, et al. Toxicity, supportive care and costs of two chemotherapy protocols for treatment of childhood ALL in Russia: BFM 90m and MB 91. *Eur J Cancer.* 1999;35:1349-1355.

10. Spinetta JJ, Masera G, Eden T, et al. Refusal, noncompliance, and abandonment of treatment in children and adolescents with cancer: a report of the SIOP Working Committee on Psychosocial Issues in Pediatric Oncology. *Med Pediatr Oncol.* 2002;38:114-117.

11. Wilimas JA, Ribeiro RC. Pediatric hematology oncology outreach for developing countries. *Hematol Oncol Clin North Am.* 2001;15:775-787.

12. Right to Health: Crossing barriers to access health in the occupied Palestinian territory 2016. Cairo: WHO Regional Office for the Eastern Mediterranean; 2017. License: CC BYNC-SA 3.0 IGO.

13. UN Human Rights Council, *Report of the Special Rapporteur on the situation of human rights in the Palestinian territories occupied since 1967,* 11 January 2016, A/HRC/31/73, available at: http://www.refworld.org/docid/56c43cf44.html [accessed November 7 2017]

14. Wazwaz N: In Gaza, kids with cancer have 'virtually no care.' One group hopes to help. NPR, December 6, 2015:http://www.npr.org/2015/12/06/458685066/in-gaza-kids-with-cancer-have-virtually-no-c are-one-group-hopes-to-help

15. World Bank: West Bank and Gaza. http://data.worldbank.org/country/west-bank-and-gaza

16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Amer Statist Assn.* 1958;53:457-481.

17. Palestine National Institute of Public Health, *Overview of Public Health in Palestine,* https://www.pniph.org/en/about/overview-of-public-health-in-palestine [Accessed August 25 2020]

18. UN office for the coordination of human affairs, *Additional treatment option available to cancer patients in Gaza amid tightening of access restrictions*, 2 June 2002, available at https://reliefweb.int/report/occupied-palestinian-territory/additional-treatment-option-available-cancer-patients-gaza [Accessed August 25 2020]

19. Harrison CJ. Cytogenetics of paediatric and adolescent acute lymphoblastic leukaemia. *Br J Haematol.* 2009;144:147-156.

20. Stock W, Sather H, Dodge RK, et al. Outcome of adolescents and young adults with ALL: a comparison of children's cancer group (CCG) and cancer and leukemia group B (CALGB) regimens. *Blood.* 2000;96:476a.