http:// ijp.mums.ac.ir
Original Article (Pages: 3381-3389)

Cost-analysis of Treatment of Pediatrics Acute Lymphoblastic Leukemia based on ALL-BFM Protocol

Hadi Hayati [1], *Abbas Kebriaeezadeh [1], Mohammad Ali Ehsani [2], Shekoufeh Nikfar [1], Azim Mehrvar[3]

[1]Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, IR Iran.
[2]Department of Pediatric Hematology and Oncology, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, IR Iran.
[3]MAHAK Pediatric Cancer Treatment and Research Center, Tehran, IR Iran.

Abstract

Background

Among all pediatric cancers acute lymphoblastic leukemia (ALL) is highly prevalent**,** but the overall cost of ALL management is not well-known**,** there is a need to assess the Berlin-Frankfurt-Munster (BFM) protocol commonly used in ALL management in Iran. So, the aim of this study was to estimate direct and indirect costs of ALL treatment among children based on the ALL-BFM protocol from the societal perspective in Iran.

Materials and Methods

A retrospective study was conducted. All pediatric patients newly diagnosed with ALL and managed by the BFM protocol from 2010-2015 were included. Finally, total costs, including direct medical costs, direct non-medical costs and indirect costs were calculated.

Results

The total direct medical cost per patient for a complete treatment period was 15,026.6 US dollars, the direct non-medical cost incurred was 1,688.9 USD and the indirect cost due to productivity loss was 932.3 USD.

Conclusion

Treatment of pediatrics ALL is less costly in Iran comparing other countries. So, physicians and policy makers and health care system administrators should devise an appropriate strategy to reduce the direct medical costs which have more economic burden special for hospitalization days and chemotherapy costs based on the findings.

Key Words: Acute lymphocytic leukemia, ALL-BFM, Cost-analysis, Pediatrics.

*Please cite this article as: Hayati H, Kebriaeezadeh A, Ehsani MA, Nikfar Sh, Mehrvar A. Cost-analysis of Treatment of Pediatrics Acute Lymphoblastic Leukemia based on ALL-BFM Protocol. Int J Pediatr 2016; 4(9): 3381-89. DOI: **10.22038/ijp.2016.7370**

Corresponding Author:

Abbas Kebriaeezadeh, PhD, Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, IR Iran.

E-mail address: kebriaee@sina.tums.ac.ir

Received date Jan 28, 2016 ; Accepted date: Mar 22, 2016

1- INTRODUCTION

More than 90% of pediatric cancer cases live in low income and developing-countries where healthcare resources are limited. In recent years, allocation decisions of treating pediatric cancers in these settings are unidentified (1). Today medical costs are increasing; the costs are attributed by both the total health care cost and the loss of productivity because of ill health status (2). Pediatric acute lymphoblastic leukemia (ALL) is the most common childhood malignancy among all pediatric cancers and is potentially curable (3). Scientific advancement in ALL management had enhanced survival from 0-5% in the 1960s to the current 80-85% (4). However since families have to pay for the total costs of therapy, high rates of treatment abandonment and refusal are experienced, mainly as a result of non-affordability (3). Entry new technologies in clinical practice depend on its impact on survival and costs. Due to the small ALL patient groups who have received it, these aspects have remained understudied (5).

The high cost of management disprivileged children in developing countries from the care (6). ALL economic burdens on the payers should be supported by sufficient evidence. Policymakers will always rely on appropriate economic data to decide on what and how to do for the prevention and management of ALL (7). In developing countries, the economic burden made many households avoid the care. On the other side, the overall cost of ALL management is not well-known by health professional, policy developers, and insurance companies. But ALL can be diagnosed at the early years of life, which can be given with supportive and/or curative intent, is considered expensive compared with that for other cancers (8). Their' goal on increasing health care coverage for ALL patients can be achieved by avoiding wastage of medical resource and decreasing medical care cost (9). Due to the disease affects quality of life and poses an economic burden on patients, payers, and society (10). In this setting the Berlin-Frankfurt-Munster (BFM) protocol is the most used in ALL care in Iran. Therefore, a study on the overall cost and individual cost of ALL management based on BFM protocol has a tremendous significance on the care (9). The improvement in survival in this protocol dragged the attention to the consequences and the overall cost of the care. Although, a lot of analysis had been done on cancer treatment cost, the direct and indirect cost of ALL management in children, is not well investigated (4).To date, no published data on the exact costs has existed for Iran which makes clear a comoerhansive cost analysis at diagnosis until completed treatment, because precise estimates of costly factors of ALL treatment have an important impact in the process of treatment by physicians and governmental and non-governmental organizations devise the allotted budget share based on cost of the health service (3).

1-1. Objective

ALL management has a direct cost from health care consumption and indirect cost from loss of productivity of caregiver relatives. Different activities have been done to contain the cost, but studies are rarely done to show the cost of all over care particularly the direct and indirect non-medical costs. Published document couldn't be found about the economic analyses of direct and indirect cost of ALL management in Iran. So, the aim of this study was to estimate direct and indirect costs of ALL treatment among children based on the ALL-BFM protocol from the societal perspectives in Iran.

2- MATERIALS AND METHODS

2-1. Patients and Methods

A retrospective study was conducted, in 2015, on children treated for ALL in MAHAK and Bahrami specialized pediatric referral hospitals by BFM protocol in Tehran. Medical records were used as a source of information. All pediatric patients newly diagnosed with ALL and managed by the BFM protocol. Patients who were diagnosed from 2010 and they completed the whole treatment until 2015. Patients with relapse and bone marrow transplantation before finishing the first line regimen were excluded. Patients were followed from admission to completion of treatment. A total of 9,758 discharge sheets of patients who finished treatment by BFM protocol were reviewed. Medical insurances, charity plans or medical university hospitals in government system had covered the costs.

2-2. Treatment of leukemia

Berlin Frankfurt Munster (BFM) protocol has shown several improvements on survival of pediatric ALL patients with different updates and modification in the protocol. From 1970 to 1976, it was performed by a clinical trial with a new intensive multi-agent strategy known as the 'West-Berlin study' preceded. The study was based on the findings from research on drug resistance and on the examination that long-term remissions of ALL can be arrived by using central nervous system (CNS) irradiation and drug combinations. The probability for event free survival (pEFS) at 8 years improved from 65.8% from a care given by ALL-BFM 81 to 75.9% in ALL-BFM 90 protocol. The protocol has been in use for the past 20 years all over in the world (11), it is also, the most commonly used protocol in Iran.

2-3. Costs

Cross-sectional study was used to identify cost. A retrospective approach was used to collect resource use and clinical data at a single point in time in 2015; and covered the five-year period prior to the dates of inclusion.

2-4. Direct costs

The direct medical cost data were abstracted from inpatient and outpatient medical records. Direct cost encompassed the cost of all inputs for diagnosis and treatment. Thus, it included general costs, costs of bed (hospital stay), diagnostic costs; laboratory tests, radiology, visit and consultation, supportive care and chemotherapy, drug, nursing, operation room, medical aids, services from non-physicians and etc. The average direct medical cost for the whole duration of treatment and care was calculated.

2-5. Direct Non-Medical Cost

Direct non-medical cost was calculated based on the result from a patient's parent self-estimate questionnaire. The questionnaire assesses non-medical expenditures for services such as transportation, taking care of dependents, accommodation and meals. The calculation of the average total cost was done by considering the number of referrals per year and expenditure at each visit (12, 13).

2-6. Indirect Cost

Productivity loss can be due to reduced productivity, because of presenteeism which is working with illness, injury, anxiety, etc. or absenteeism (14, 15). The cost of productivity loss by ALL patients' proxies was calculated by using the friction cost method. This method considers 80% and 40% average wage for loss of workdays and leisure time lost caring for patients respectively (16, 17). The cost data were collected, after informed consent was obtained, through face-to-face or telephone interview with the patient's parents or children. The number of missed workdays and the average net daily wage were recorded for each patient.

2-7. Ethical considerations

This study was approved by the Research Ethics Board of Tehran University of Medical Sciences, Tehran, Iran.

2-8. Statistical analysis

Adjustment for inflation based on average annual inflation rates in health care from January 2010 to October 2015 was done. For the sake of international comparison, the cost was changed from Iranian currency (Rials: 35,000 IRR≈1 USD) to USD by taking the average annual exchange rate (18). Microsoft excels and SPSS-16, were used for data analysis. P-value less than 0.05 were significant. Finally all collected data were analyzed by specialists in Statistics, Health economics, Pharmacoeconomics and oncology.

3- RESULTS

In this study we tried to calculate three variables affecting on the total cost of pediatrics ALL treatment includes direct medical costs, direct non-medical costs and indirect costs. In the beginning according to the demographic characteristics on **Table.1**, the mean age of the entire sample was 9 ± 3.4 years. The prevalence of ALL in boys was higher than girls (55% Male, 45% Female). The majority of parents (73%) had nonacademic education. The average length of stay in hospital was 123±13 days. The average monthly income was 302 US dollar. Finally, more than 96% of families had one kind of health insurances. First final cost analysis shows the total direct medical cost per patient for the complete treatment period was 15,026.6 USD; while most of the costs were spent on inpatient bed service (5,452 ± 1,352 USD). The drug expenditures were the second (4,724 ± 2,351 USD) largest contributors for the medical cost, whereas diagnostic services had the lowest cost (about 150.1 ± 58 USD) (**Table.2 and Figure.1**).

The direct non-medical cost incurred was 1,688.9 USD, when most of the cost (675.5 USD) was used for transportation (**Table.3**).

The indirect cost due to productivity loss was 932.3 USD. Presenteeism costs was 540.8 USD while absenteeism accounted for 391 USD (**Table.4**).

Finally, **Figure.2** shows the percentages of types of Costs by BFM-ALL treatment protocol. The medical cost is higher than any other costs of therapy. Also, the total cost of treatment of pediatric acute lymphoblastic leukemia based on ALL-BFM protocol as the main finding of this research is 17,647.5 USD in Iran, which is the sum of other costs (**Table.5**).

Table-1: Demographic characteristics of patients and parents by BFM protocol for ALL in Iran

Variables		BFM ALL
Number of patient		203
Children age (Mean ± SD)		9 ±3.4
Gender of Children (%)	Male	56(%)
	Female	44(%)
Education Level of parents (%)	Non-academic	73(%)
	University education	22(%)
Average length of stay,day (Mean ± SD)		123±13
Average monthly income, Dollarl (Mean ± SD)		302±121
Having one health insurance		96 (%)

SD: Standard deviation.

Table-2: All direct medical costs of patients by BFM-ALL treatment protocol (in 2015 US dollars)

Type of cost		Cost (Mean-USD)	SD	%
1	Bed	5452	2563	36.2
2	Drug	4724	2351	31.4
3	Lab test	2058.5	412	13.6
4	Visit & Consultation	1408.7	321	9.3
5	Operation room	464.9	125	3
6	Medical supplies of part	443.9	237	2.9
7	Nursing	323.8	89	2.1
8	Diagnostic services	150.1	58	1
Total		15026.3	4859	100

SD: Standard deviation.

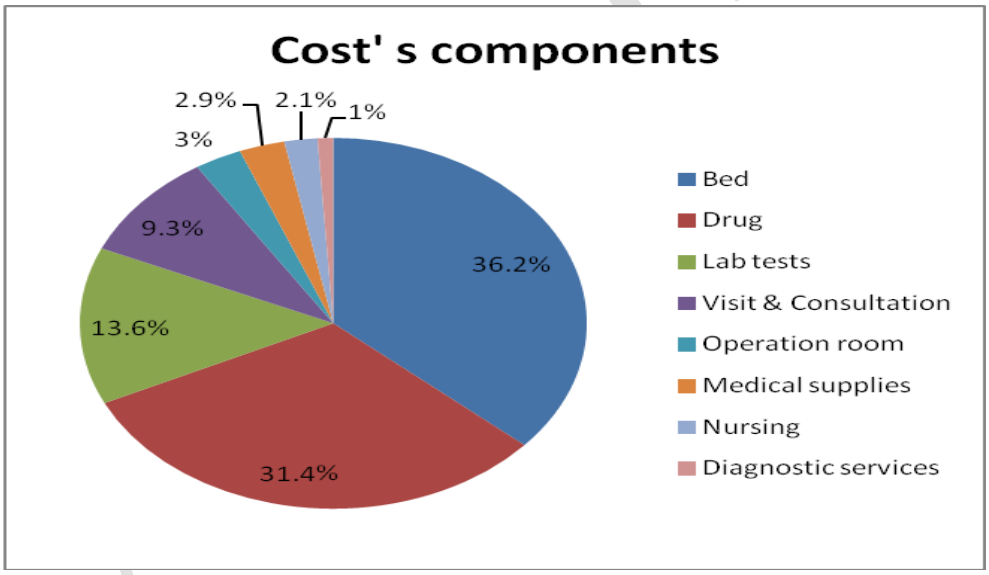

Fig. 1: The percent of direct medical cost' components of patients by BFM-ALL treatment protocol

Table-3: Direct non medical costs of patients by BFM-ALL treatment protocol (in 2015 US dollars)

Type of cost		Cost (Mean-USD)	SD	%
1	Transportation	675.5	235	39.9
2	Meals	337.7	136	19.8
3	Accommodation	506.6	214	29.9
4	Other	168.8	98	10
Total		1688.9		100

SD: Standard deviation.

Table-4: Indirect costs of patients by BFM-ALL treatment protocol (in 2015 US dollars)

Type of cost		Cost (Mean-USD)	SD	%
1	Absenteeism	391.5	205	41.9
2	Presenteeism	540.8	286	58.1
Total		932.3		100

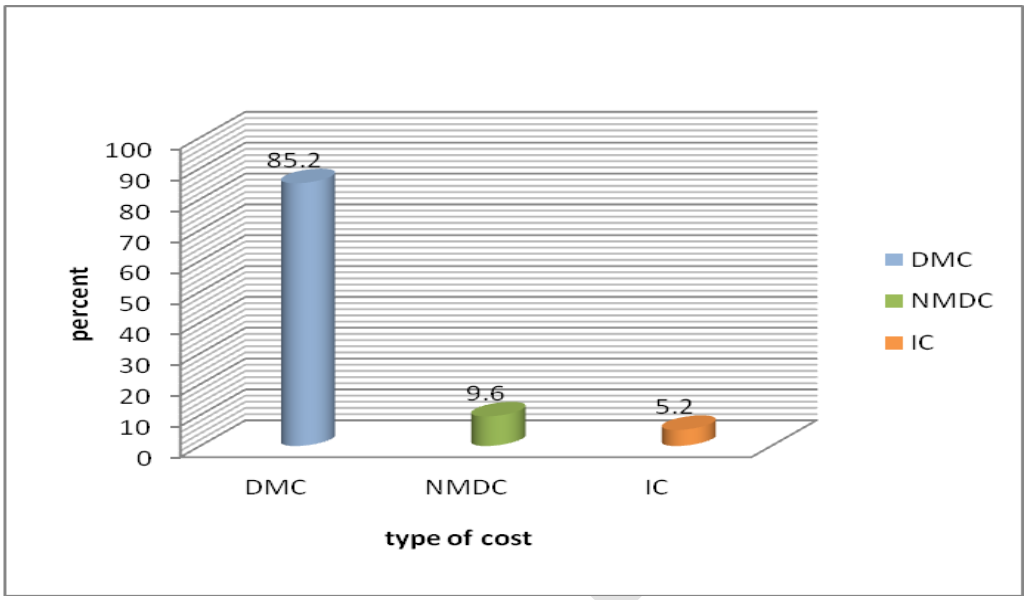

Fig.2. Direct Medical Costs, Direct Non-medical Costs, and Indirect Costs as a Percentage of Total Cost of patients by BFM-ALL treatment protocol

Table-5: Types of costs of patients by BFM-ALL treatment protocol (in 2015 US dollars)

Type of cost	Cost (Mean-USD)	%
DMC	15026.3	85.2
NMDC	1688.9	9.6
IC	932.3	5.2
Total	17647.5	100

DMC: Direct Medical Costs; DNMC: Direct Non-medical Costs; IC: Indirect Costs.

4- DISCUSSION

This study was the first comprehensive study, which includes the direct medical and non-medical, and indirect cost at the societal perspective of ALL management at national level. The present study revealed the financial burden of ALL management in the country, particularly in the health system and families with affected children. According to the demographic characteristics, the mean age of the entire sample was 9 ± 3.4 years, due to were excluded children under 5 years age and the prevalence of ALL in boys was higher than girls (55% Male, 45% Famale), anyway it's similar to other studies (19-22). The total treatment cost per patient was 17,647.5 USD. The whole treatment of ALL in children required about 123 hospital days based on BFM protocol. However, it is important to note based on the Iranian health system, when considering the private medical tariffs the

direct medical cost of treatment is estimated manifold in Iran (19). There was no comprehensive studies include non-medical, and indirect costs like these findings to compare.

Direct medical costs had the greatest share of total costs about 15,026.3 USD (80.2%), and the cost of hospital bed took the larger part of the total direct medical cost (36.2%). Drug expenditures hold 31.4% (4,724 ± 2,351 USD) of the direct medical cost. The BFM protocol needs for long hospitalization led to inflated medical cost. The cost components, drug expenditure and hospital bed, were the main contributors to high medical cost in similar studies (18-21).

So, it seems that one of the important ways to lower the treatment costs would be to reduce inpatient days by treating patients in the outpatient clinic as much as possible. The current finding of direct medical cost was higher than the direct medical cost of unidentified protocol studied by Davari et al. in Iran. In this unidentified protocol, the median of the direct medical cost per patient was approximately 6,600 USD (19). The mean total cost of ALL management through BFM protocol was US$ 88, 480 in Canada and several European countries (20).

A higher cost was observed from a study in Finland (US$ 103, 250 USD) (21). The median hospitalization cost of Non-High Risk Acute Lymphoblastic Leukemia management through modified ALLIC BFM 2002 in China was USD 9,900 (22). Generally, the cost of ALL management by BFM protocol in Iran was far cheaper than high- income countries. This difference might be due to the use of more generic products in Iran.

The direct nonmedical costs (1,688.9 USD) were contributed by transportation, meals, and accommodation. Transportation cost had taken the biggest share (39.9%). The increased contribution of transportation might be due to the fact that some patients were coming outside of Tehran, where some provinces are very far from the city. A similar study by Ghatak et al. in North India found USD 207 as a total nonmedical cost while food was the main source of expenditure (23). This difference might be due to more health insurance coverage, better facilities and a relatively higher income in Iran. In the current study indirect costs (932.3 USD) had the lowest share of the total cost (5.2%). However, similar studies in other countries showed devastating outcome. Ghatak et al. from India reported 72 % families suffered the loss of income, 34 % fathers lost their jobs; and Limburg et al. found 64% of mothers and 16% of fathers left their job after their child's diagnosis (24). Generally, families with a child diagnosed with cancer, have a reduced income because of reduced working hour or leaving their job (25).

The cost of absenteeism (391.5 USD) was low in this study. The presenteeism costs (58.1%) had a greater share of the total indirect costs. The difference in indirect cost might be due to the differences in social structure and health system between the countries. Indirect costs like other costs decrease with the improvement of care and effectiveness of treatment. It is also, a well-known fact that indirect costs are affected by the productivity of the country.

4-1. Limitations of the study

Although this is the first study evaluating whole related costs of treatment of childhood Acute Lymphoblastic Leukemia in Iran, there are some limitations.

As there were not an integral data regarding of direct nonmedical and indirect costs in the documents. also it is possible that missing data in medical records had not led to an exact estimation of the costs about the data were collected from medical records.

5. CONCLUSION

The results showed that distraction technique had a good effect on the intensity of pain in children. Given the need for pain control and its effects on the course of treatment, further studies are needed to be done.

6- CONFLICT OF INTEREST

Professor Azim Mehrvar works at MAHAK hospital where this work was carried. There is no conflict of interest for other authors.

7- ACKNOWLEDGMENTS

The authors would like to acknowledge staffs working in the Hospitals and also, for families of children involved data collection. This paper resulted from a Ph.D. thesis of the first author and was supported financially by Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran- Iran.

8- REFERENCES

1. Bhakta N, Martiniuk AL, Gupta S, Howard SC. The cost effectiveness of treating paediatric cancer in low-income and middle-income countries: a case-study approach using acute lymphocytic leukaemia in Brazil and Burkitt lymphoma in Malawi. Arch Dis Child 2013; 98(2): 155-60.

2. Kalantari H, Davari M, Akbari M, Hejazi SM, Kalantari M, Zakerin S, et al. The estimation of direct medical costs of treating patients with chronic hepatitis B and C in Iran. Int J Prev Med 2012; 3(3):191–6.

3. Islama A, Akhterb T, Eden C. Cost of treatment for children with acute lymphoblastic leukemia inBangladesh. Journal of Cancer Policy 2015; 6: 37–43.

4. Schrappe M, Hunger SP, Pui CH, Saha V, Gaynon PS, Baruchel A, et al. Outcomes after induction failure in childhood acutelymphoblastic leukemia. N Engl J Med 2012; 366(15):1371-81.

5. Van de Velde AL, Beutels P, Smits EL, Van Tendeloo VF, Nijs G, Anguille S, et al. Medical costs of treatment and survival of patients with acute myeloid leukemia in Belgium. Leukemia Research 2016; 46: 26-9.

6. TangY, Xu X, Song H, Yang S, Shi S, Wei J. Long-term outcome of childhood acute lymphoblastic leukemia treated in China. Pediatr Blood Cancer 2008; 513:380–386.

7. Keshavarz K, Kebriaeezadeh A, Meshkini AH, Nikfar S, Mirian I, Khoonsari H. Financial perspective of private pharmacies in Tehran (Iran); is it a lucrative business? Daru 2012; 20(1):62.

8. Wang HI, Aas E, Howell D, Roman E, Patmore R, Jack A, Smith A. Long-term medical costs and life expectancy of acute myeloid leukemia: A probabilistic decision model. Value in Health 2014; 17: 205-14.

9. Pui CH, Crist WM. Biology and treatment of acute lymphoblastic leukemia. J Pediatr 1994; 124: 491-503.

10. Frey S, Blankart CR, Stargardt T. Economic Burden and Quality-of-Life Effects of Chronic Lymphocytic Leukemia: A Systematic Review of the Literature. PharmacoEconomics 2016; 34(5): 479-98.

11. Schrappe M, Reiter A, Zimmermann M, Harbott J, Ludwig WD, Henze G, et al. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Berlin-Frankfurt-Münster.Leukemia 2000; 14(12):2205-22.

12. Kavosi Z, Zare F, Jafari A, Fattahi MR. Economic burden of hepatitis B virus infection in different stages of disease; a report from southern iran. Middle East J Dig Dis 2014; 6(3):156–61.

13. Ong SC, Lim SG, Li SC. How big is the financial burden of hepatitis B to society? A cost-of-illness study of hepatitis B infection in Singapore. J Viral Hepat 2009; 16(1):53–63.

14. Liljas B: How to Calculate Indirect Costs in Economic Evaluations. PharmacoEconomics 1998; 13:1–7.

15. Koopmanschap MA, Rutten FFH, Van Ineveld BM, Van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ 1995; 14:171–89.

16. Ganjali M, Baghfalaki T. Bayesian analysis of unemployment duration data in presence of right and interval censoring. JRSS 2012, 5(1):17–32.

17. Statistical center of Iran. Available at: http://www.amar.org.ir.

18. Central Bank of Iran. Available at: www.cbi.ir/exrates/rates_fa.aspx.

19. Davari M, Moafi A, Yarmohammadian MH, Khayyam Haghighi E. The Direct Medical Costs of Acute Lymphocytic Leukemia (ALL) In Children in

20. Isfahan Province. Health Inf Manage 2015; 11(7):1046.

21. Rae C, Furlong W, Jankovic M, Moghrabi A, Naqvi A, Sala A, et al. Economic evaluation of treatment for acute lymphoblastic leukaemia in childhood. European Journal of Cancer Care 2014; 23: 779–85.

22. Rahiala J, Riikonen P, Kekalainen L, Perkio M. Cost analysis of the treatment of acute childhood lymphocytic leukaemia according to Nordic protocols. Acta Paediatrica 2000; 89: 482–87.

23. Luo XQ, Ke ZY, Guan XQ, Zhang YC, Huang LB, Zhu J. The Comparison of Outcome and Cost of Three Protocols for Childhood Non-High Risk Acute Lymphoblastic Leukemia in China. Pediatr Blood Cancer 2008; 51:204–9.

24. Ghatak N, Trehan A, Bansal D. Financial burden of therapy in families with a child with acute lymphoblastic leukemia: report from north India. Supportive Care in Cancer 2016; 24: 103-108.

25. Limburg Hac, Shaw AKa, McBride MLb. Impact of childhood cancer on parental employment and sources of income: A Canadian pilot study. Pediatric Blood and Cancer 2008; 51(1): 93-8.

26. Miedema Bad, Easley Ja, Fortin Pb, Hamilton Ra, Mathews M. The economic impact on families when a child is diagnosed with cancer. Current Oncology 2008; 15(4): 8-13.