Treatment Costs for Pediatrics Acute Lymphoblastic Leukemia; Comparing Clinical Expenditures in Developed and Developing Countries: a Review Article

Hadi Hayati¹, Abbas Kebriaezadeh¹, *Mohammad ali Ehsani², Shekoufeh Nikfar¹, Ali Akbari Sari³, Mehdi Troski¹, Bereket Molla Tigabu⁴

¹Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, IR Iran. ²Department of Pediatric Hematology and Oncology, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, IR Iran. ³Department of Health Management and Economics, Tehran University of Medical Sciences, Tehran, IR Iran. ⁴International Campus, Department of Pharmacoeconomics and Pharmaceutical Management Haramaya University School Of Pharmacy.

Abstract

Background
Pediatric acute lymphoblastic leukemia (ALL) is the most common, yet curable childhood malignancy within the pediatric cancers; but in most developed and developing countries cost of cancer treatment in children with ALL is high. So, we specified the range of expenses for the treatment of pediatric cancer and compared the results in developed and developing countries.

Materials and Methods
To evaluate treatment costs in childhood ALL, a review was taken place through published papers during the years 2000 to 2015. We searched multiple well known databases such as Medline, Scopus, ISI Web of Science and Google Scholar on January 2015 with "cost effectiveness", "cost utility", "cost minimization", "cost analysis", "economic evaluation", "childhood", "acute lymphoblastic leukemia", and "ALL" as our keywords.

Results
Regarding the reviewed evidence the essential result was that the total costs for treatment of pediatrics ALL in developing countries such as Asian countries were considerably lower than the costs reported from high income countries in Europe and North America. So different protocols were performed to treat ALL and this matter was significant due to the different durations of hospitalization.

Conclusion
According to the results, the total costs for treatment of pediatrics ALL in developing countries were considerably lower than the costs reported from high income countries.

Key Words: Acute Lymphocytic Leukemia, Children, Costs, Developed Countries, Developing Countries.


*Corresponding Author:
Mohammad ali Ehsani: Department of Pediatric Hematology and Oncology, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, IR Iran. Tel.: 0098-21-73013406.
Email: maehsani@gmail.com
Received date Sep.23, 2016; Accepted date: Oct. 22, 2016
1- INTRODUCTION

Most pediatric cancers live in low and middle-income countries that lack healthcare resources. In these situations, the Allocation of resources for treating pediatric cancer is not acknowledged (1). Today the increased medical expenses are due to both the health care costs and the loss of productivity caused by a low health status (2, 3). Also, modern technologies in the health sector effect on both survival and costs (4). Pediatric acute lymphoblastic leukemia (ALL), is the most common, yet curable childhood malignancy within the pediatric cancers (5, 6). But in most developed and developing countries cost of cancer treatment in children with ALL is high. Also, in developing countries, high expenses of treatment for many patients with ALL lead to unfinished treatment (7-9). The small ALL patients who received treatment have caused the comprehensive cost analysis to remain understudied (10).

Financial burdens on the ALL patients should be supported by providing sufficient evidences. Policymakers and physicians should always appropriate economic data when they are managing ALL (11). Currently, there are no published comprehensive studies to compare the costs of treatment for children with acute lymphoblastic leukemia in developed and developing countries. This is of importance, because a precise comparison of costs on ALL treatment has an impact on the process of treatment by physicians and governmental and non-governmental organizations devising the allotted budget share based on the cost of the health service, especially in developed and developing countries (12, 15). But, a critical evaluation of the costs required to treat these conditions has not been done and the case for their cost analysis has not been made. We specified the range of expenses for the treatment of pediatric cancer and compared the results in developed and developing countries to guide prioritization efforts for ALL in that countries.

2- MATERIALS AND METHODS

2-1. Data sources and searches

To evaluate treatment costs in childhood ALL, a systematic review was taken place through published papers during the years on April 2000 to January 2015. We searched multiple well known databases such as Medline, Scopus, ISI Web of Science and Google Scholar with "cost effectiveness", "cost utility", "cost minimization", "cost analysis", "economic evaluation", "childhood", "acute lymphoblastic leukemia", and "ALL" as our keywords.

2-2. Literature search

Through the database search we identified 408 studies in MEDLINE, 380 studies in Scopus, 119 studies in ISI Web of Science and 881 studies in Google Scholar. After identifying and removing duplicates, the titles and abstracts were intently analyzed. 17 of the studies were identified for full-text analysis. From these, 9 studies were excluded, which ultimately lead to the inclusion of seven studies in this review (Figure.1). The features of all the eligible studies show that for the economic component of the review, after reviewing the articles, most were specifically relevant to the cost analysis studies of ALL in children. In addition, other characteristics show that most of the studies have less than one hundred eligible patients with up to 15 years of age. Also, the retrospective method of data collection was used from medical records. Four of the studies were conducted in developing Countries like Iran, China, Bangladesh and Shanghai-China, also other studies were in developed Countries like Netherlands, Finland and Canada. Different protocols
were performed to treat ALL and this matter was significant due to the different durations of hospitalization (Tables 1, 2), please see the end of paper.

**Fig. 1**: Process of study selection for eligible studies

2-3. **Process of study selection**

Our inclusion criteria were English language studies on cost of childhood ALL and the exclusion criteria were proceedings, biochemical, pharmacokinetic and non-clinical studies, animal studies and clinical trials. After eliminating duplicates, the titles and abstracts of the articles were assessed by two of the authors independently in order to rule out irrelevant reports based on the inclusion and exclusion criteria. Through discussion the differences in opinion were resolved and a consensus was reached. After that the full texts of the included articles were double checked and examined by detail to obliterate some other reports regarding the exclusion/inclusion criteria. Also, a data extraction sheet was conducted to standardize the items for extraction.
3- RESULTS

3-1. Results in developed Countries

In most of the studies cost components included general administrative and technical service costs, bed service costs (including food, transport and cleaning), capital costs, also laboratory, radiology and therapy costs (cytostatic drugs, irradiation, operations, procedures, transfusions of red blood cells and platelets, antibiotics, antifungals, antiviral drugs, antiemetics, fluids and total parenteral nutrition).

The mean of the total direct cost per patient ranged from 163,350±38,245 US Dollar (USD) in the Netherlands and 103,250±23,875 USD in Finland (12, 15). The bulk of the total costs in almost all the studies were associated with hospitalization and drugs it means the factors were main components of entire costs. The least cost in almost all of the studies was associated with blood products, imaging and the operation room. General treatment costs were greatest during the induction phase with a round of 33% to 35% of the total costs in Finland and Netherlands (12, 15).

In Rae’ study inpatient stays accounted for the most among all treatment costs for both Berlin-Frankfurt-Munster(BFM) (mean inpatient cost =60,855±11,785 USD) and Dana-Farber Cancer Institute(DFCI) (mean inpatient cost = 59,321±12,896 USD) strategies. Altogether, the mean number of inpatient and outpatient days was 44 and 123, respectively. The analysis of the discounting rates showed difference between strategies in total treatment costs at 0% and 3% (16). In Finland, the majority of the total costs were associated with hospital services. The Finnish study reported a mean number of inpatient and outpatient days of 129 and 39, respectively (12). This matter created in the Fin’s study is probably due to a shift in treatment from inpatient stays to outpatient visits. In the Netherlands study (15), higher costs were related to diagnostic testing (for minimal residual disease), medication [PEG L Asparaginase (pegaspargase)], and more hospital days, that were deflected by longer event-free survival.

3-2. Results in developing countries

The mean of the total direct cost per patient ranged from 6,139±458 USD in Iran to 4,443±896 USD in Bangladesh (13-14). In China the hospitalization cost was the lowest in the Economic Protocol due to less intense chemotherapy, lower incidence of treatment-related complications and a shorter duration of total hospital days. The hospitalization costs were higher on China-98 protocol than on modified protocol, since patients on China-98 protocol had several courses of intensification chemotherapy in hospital during maintenance. This report showed that hospitalization costs for childhood ALL exceeded 10,000 USD (17). Based on the article’s explanation however, in China the fee of blood product transfusion was the highest on modified ALLIC, in which the induction and reinduction chemotherapy were the most intense protocols and resulted with more severe bone marrow suppression, and thus more transfusions of pack red cells and platelets were needed (17).

In the study taken place in Shanghai, the average overall expense of childhood ALL per person was approximately 11,000 USD. In this article all local children in Shanghai can receive support from birth through the government welfare system. In this study, the highest cost was 49,848 USD and the lowest cost was only 5,597 USD. But the medical costs increased sharply once a patient had severe complications. The results show that medicine costs were the main
expenditure for the treatment of childhood ALL. Although, the overall costs decreased because the cost was lower in the clinics rather than the hospital (10). In the study taken place in Iran the average of the direct medical costs per patient were around 3,885 USD for the main protocols in treatment and 2,228 USD for the complementary therapies based on the public medical tariffs. The medication costs were the major cost components of the treatment (365 USD); and the total direct medical costs of ALL based on public medal tariffs were equal to 6,139 USD. Although, considering the hidden subsidy in the public sector, it seems that the figure 17,428 USD is more realistic for costs of managing ALL patients in Iran (14). In Bangladesh the drug costs were the major cost components of the treatment (1,571 USD), and the total cost was 4,443 USD. There are no current provisions of a comprehensive national health insurance scheme for patients in Bangladesh. So their families have to purchase the medicine directly from a pharmacy. According to the information from the health system in Bangladesh every patient studied was admitted to "free beds" (food and bed free of cost). Also, the medical consultations are cost free. Parents did buy all of the needed drugs from outside pharmacies, but blood products were collected from the hospital transfusion medicine department and there is a hospital cost subsidy on these products for all patients (13).

4- DISCUSSION

According to the discussions in the main text of these articles, the incidence of childhood cancer is rising in developing countries (13, 14, 18, 19), along with deaths and high treatment costs and a low income of families. Thus a large number of children living in such low and middle income countries are prohibited from obtaining appropriate and complete treatment. Although the treatment of childhood ALL has improved with a consistent therapy using specified protocols, but after achieving complete recovery, patients require phases of intensive therapy and then an outpatient treatment. Therefore non-compliance with treatment protocols, especially due to the "financial abandonment", is a serious problem (20-22); so, with the consideration of the high costs of treatment in the developed countries, the authors believe that the potentially curative treatment of childhood ALL with a result of a long and relatively good quality of life (23) is not expensive.

The treatment of childhood ALL costs around 100,000 USD per patient based on the results of the studies. Since almost 80% of the childhood ALL are long-term survivors with a good quality of life, the expenses in the terms of gained quality adjusted years are reasonably low, unlike the developing countries. Hisashige showed that the expenses for prevention and treatment of complications were high during the process of treating leukemia, so the overall medical cost of childhood ALL could be reduced to less than 11,000 USD in developing countries such as China. Every pediatric cancer center in developing countries should have data management programs that facilitate careful documentations of medical costs and outcomes; this kind of program would allow doctors to pay more attention to revising treatment costs effectively as well as potentially curing the most possible number of children with cancer chemotherapy at their homes (24, 25).

4-1. Limitation of study

We could not find studies that just about costing in pediatrics ALL, so we considered any economic evaluation in this field to include in this study.

5- CONCLUSIONS
In conclusion the essential result was that the total costs for treatment of pediatrics ALL in developing countries like countries in Asia were considerably lower than the costs reported from high income countries in Europe and North America. Furthermore the most important extra costs in patients with ALL were increased inpatient days and cytostatic drug costs, and also induction therapy accounted for around one third of all costs, so a wide variation can be found in the average cost per patient on each protocol.

The main reason for this is due to the use of different treatments and hospitalization in the health systems of different countries. It seems that the only way to decrease the treatment costs would be to reduce inpatient days by treating patients in the outpatient clinic as much as possible or attempt to reduce hospital costs by administering selected chemotherapy at home. It should be noted that, the cost of ALL treatment is unpredictable because of the individual differences. We could not compare those results together completely because the indications for admission and in-hospital days differ in health systems all over the world.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

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. The authors would like to appreciate all who helped conducting this study.

8- REFERENCES


**Table-1**: General characters of all included eligible studies

<table>
<thead>
<tr>
<th>Row</th>
<th>Study</th>
<th>Type</th>
<th>Country</th>
<th>Number of patients</th>
<th>Method of cost data collection</th>
<th>Duration of study</th>
<th>Mean duration of hospitalization</th>
<th>Age</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Y. Liu (2009)</td>
<td>Cost analysis</td>
<td>Shanghai</td>
<td>45</td>
<td>Retrospective</td>
<td>2005-2006</td>
<td>75.8_37.9</td>
<td>The median= 5 years (15 months to 14 years)</td>
<td>ALL-2005 protocol</td>
</tr>
<tr>
<td>3</td>
<td>C.RAE (2014)</td>
<td>Economic evaluation</td>
<td>Ontario</td>
<td>66 BFM and 28 DFCI</td>
<td>Retrospective from the medical record</td>
<td>1996 -2010</td>
<td>Mean inpatient=44 and outpatient=123</td>
<td>More than 5 years of age</td>
<td>(BFM) and (DFCI)</td>
</tr>
</tbody>
</table>

*Nordic Society of Pediatric Hematology and Oncology; Berlin-Frankfurt-Munster; Dana-Farber Cancer Institute; USD: United States dollar.
### Table-2: The investigated factors of all included eligible studies

<table>
<thead>
<tr>
<th>Row</th>
<th>Study</th>
<th>The most cost components</th>
<th>The least cost components</th>
<th>Total cost per patient US $</th>
<th>Induction cost</th>
<th>Discount rate</th>
<th>Perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>J.Rahiala (2000)</td>
<td>54,974</td>
<td>Cytostatic drugs for 13%, 18,075</td>
<td>103,250</td>
<td>36,254</td>
<td>35%</td>
<td>-----</td>
</tr>
<tr>
<td>2</td>
<td>Y. Liu (2009)</td>
<td>478.41 Hospital bed/daycare</td>
<td>Blood products 788.7</td>
<td>11,000</td>
<td>2,752</td>
<td>-----</td>
<td>Hospital</td>
</tr>
<tr>
<td>3</td>
<td>C.RAE (2014)</td>
<td>Hospital services</td>
<td>-----</td>
<td>BFM (88 480) DFCI (93 026)</td>
<td>-----</td>
<td>5%</td>
<td>Hospital budget system,</td>
</tr>
<tr>
<td>5</td>
<td>Raphaele R.L (2011)</td>
<td>Hospital admissions ALL 9 (43.2%) 50,097 and ALL 10 6,276 - 40.6% overall costs</td>
<td>Imaging ALL 9:1,378 (1.2%) ALL 10:1,740 (1.1%)</td>
<td>115,858 USD (ALL 9) and 163,350 USD (ALL 10)</td>
<td>For both accounted 33% of total costs</td>
<td>4%</td>
<td>Hospital perspective</td>
</tr>
<tr>
<td>6</td>
<td>M.Davari (2014)</td>
<td>Medication (365USD)</td>
<td>OR (5 USD)</td>
<td>6139 USD</td>
<td>-----</td>
<td>Inflation rate 41%</td>
<td>Public medical tariffs</td>
</tr>
<tr>
<td>7</td>
<td>A.Islama (2015)</td>
<td>(Drugs =1571) 48.6%</td>
<td>Food and bed free. Blood products 0.6% of all costs.</td>
<td>4443 USD</td>
<td>285 USD to 398 USD</td>
<td>-----</td>
<td>Hospital perspective</td>
</tr>
</tbody>
</table>

OR: Odds ratio; USD: United States dollar.