IRANIAN JOURNAL OF BLOOD AND CANCER

The Official Journal of

Iranian Pediatric Hematology and Oncology Society (IPHOS)

Volume 8, Number 2, June 2016 ISSN: 2008-4595

"Iranian Journal of Blood and Cancer" is published by "Iranian Pediatric Hematology and Oncology Society (IPHOS)" in collaboration with "Iranian Blood Transfusion Organization (IBTO)"

"IJBC" is approved as an "Academic Research Journal" by Medical Journal Commissions of the "Ministry of Health" and Medical Education of Islamic Republic of Iran".

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Postal Code: 1419783311
Tel/Fax: +98(21)66912679
Website: www.ijbc.ir
Email: Info@ijbc.ir

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Iranian Journal of Blood and Cancer
Volume 8, Number 2, June 2016

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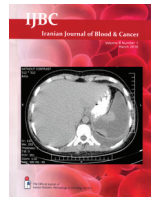

REVIEW ARTICLE

Role of Stem Cell Transplantation in the Treatment of Burkitt Lymphoma; A Systematic Review

Soheila Zareifar[1], Babak Abdolkarim[2]*, Mohamadreza Bordbar[1], Mehran Karimi[3], Fazl Saleh[4], Omidreza Zekavat[1]

1. Associate Professor of Pediatric Hematology-Oncology, Department of Pediatrics, Shiraz University of Medical Sciences, Shiraz, Iran
2. Assistant Professor of Pediatric Hematology-Oncology, Lorestan University of Medical Sciences, Khoramabad, Iran
3. Professor of Pediatric Hematology-Oncology, Department of Pediatrics, Shiraz University of Medical Sciences, Shiraz, Iran
4. Fellowship of Pediatric Hematology-Oncology, Department of Pediatrics, Shiraz University of Medical Sciences, Shiraz, Iran

ARTICLE INFO

Article History:
Received: 12.12.2015
Accepted: 10.03.2016

Keywords:
Hematopoietic stem cell transplantation
Burkitt lymphoma
Mature B cell leukemia
Autologous transplantation
Allogenic transplantation

*Corresponding author:
Babak Abdolkarimi, MD
Address: Shahid Madani hospital, Lorestan University of Medical Science, Khoramabad, Iran
Tel: +98 918 3605274
Email: b.abdolkarimi@yahoo.com

ABSTRACT

Background: Burkitt lymphoma is a common subtype of non-Hodgkin lymphoma in children. It has a rapid and aggressive clinical course with frequent involvement of bone marrow and central nervous system. Systemic chemotherapy is the mainstay of the treatment for this malignancy in children. In this systematic review, we discuss autologous and allogeneic hematopoietic stem cell transplantation (HSCT) and its indications in pediatric patients with Burkitt lymphoma.
Methods: The Medline (PubMed) database was searched using all keywords and phrases. The studies were identified by utilizing a combination of MeSH terms, such as Burkitt lymphoma, stem cell transplantation, autologous transplantation and allogeneic transplantation. Articles which were not published as full articles (conference proceedings excluded) were excluded. Relevant articles published during 2000-2015 were included.
Results: 13 articles met the inclusion criteria and were discussed.
Conclusion: Both autologous and allogeneic HSCT may improve survival in patients with BL. Autologous HSCT is mainly considered for patients with high-risk features of BL at presentation; however, allo-HSCT with non-myeloablative conditioning regimens are preferred for advanced stages and relapsed/refractory disease.

Please cite this article as: Zareifar S, Abdolkarimi B, Bordbar MR, Karimi M, Saleh F, Zekavat OR. Role of Stem Cell Transplantation in the Treatment of Burkitt Lymphoma; A Systematic Review. IJBC 2016; 8(2): 29-32.

Introduction

Burkitt lymphoma (BL) is one of the most aggressive types of lymphoma, classified as high grade non-Hodgkin's lymphoma (NHL) according to the REAL classification.[1] Its growth rate is very rapid and doubling time of the tumor is very short. It is usually treated with intensive chemotherapy which gives satisfactory results especially in the group of patients who have good initial response.[2]

The ideal salvage strategy for patients with BL with partial remission or relapsed disease is unknown. Combination salvage chemotherapy is usually attempted. However, very few patients with relapsed BL achieve a meaningful response regardless of the chemotherapy agent used.[3]

Autologous or allogeneic stem cell transplantation (ASCT or Allo-SCT) is recommended; however, the role of HSCT in BL is not well defined since there are limitations such as chemotherapy induced toxicity during conditioning and before HSCT. Transplant-related toxicity, particularly in patients who have received prior multiple intensive chemotherapy is also a poor determining factor.[4] Transplant-related mortality in the group of patients who underwent allogeneic SCT after failure of autologous transplantation approached 50% in one report.[5] Since HSCT in the management of BL is a challengeable topic in adults and pediatric oncology, we

aimed to perform a systematic review to find the best up-to-date available data in the literature.

Methods

The research team initially drew up a study protocol aimed at addressing the research issues raised for patients with BL or leukemia who need HSCT. A systematic search was undertaken. Two or more members of the review team reviewed all references. The Medline (PubMed) database was searched using all keywords and phrases. The studies were identified by utilizing a combination of MeSH terms, such as Burkitt lymphoma, stem cell transplantation, autologous transplantation and allogeneic transplantation. Articles which were not published as full articles (conference proceedings excluded) were excluded. Articles which addressed the clearly focused questions, those to minimise bias, relevant studies, publication dates between 2000-2015, randomized clinical trials (RCT) and other types of original articles published in English and peer-reviewed journals were selected. Recommendation Report SCT-4, a comprehensive guideline regarding HSCT in lymphoma which is a quality Initiative of the Program in Evidence-Based Care (PEBC) in Cancer Care Ontario of Canada and recommendations in 3rd WBMT Scientific Symposium in Cape Town on Nov 2014 were also are included. We decided to evaluate the quality of the studies for methodology, sampling, randomization and examined four potential sources of bias including; study participation, study attrition, confounding variables and measurement of outcomes.

Results

We searched the Medline (PubMed) electronic database by using a broad search strategy. Two reviewers independently screened the list of references to assess their eligibility for inclusion in consultation with another reviewer. Meanwhile, studies/patients meeting all of the following criteria were included in this review: 1) patients who underwent the first transplantation and 2) availability of detailed patients' characteristics and outcome data such as relapse-free survival (RFS), overall survival (OS), relapse rates (RR) and non-relapse mortality.

Finally, 13 main articles were found to form the basis for this narrative review. The flow diagram of the search study and review articles is shown in figure 1.

Discussion

The optimal salvage therapy for patients with relapsed Burkitt lymphoma is unknown.[3] Patients with relapsed/primary refractory B-NHL/B-ALL have a poor prognosis with current treatment approaches, while the patients sensitive to salvage therapy have an acceptable chance to achieve a sustained complete second remission with high-dose chemotherapy and HSCT.[6,7]

Actually, the modern immune-chemotherapy with Rituximab and CNS prophylaxis has resulted in dramatic improvement in the management of patients with NHL, with similar reports to those obtained from less intensive regimens, survival rates close to 90%.[8,9]

There has been a progressive reduction in the use of auto-HSCT as consolidative therapy in first complete remission (CR).[9] Nevertheless, for patients with high risk characteristics including elevated LDH levels, bulky disease at presentation, involvement of bone marrow or CNS or relapsed/refractory disease, HSCT should be considered.[10-14]

In relapsed patients, the disease can be salvaged with high-dose chemotherapy and autologous stem cell transplantation which results in 37% long-term disease-free survival depending on the disease status at the time of transplantation.[15]

Transplant-related toxicity, particularly in patients who have received prior multiple intensive chemotherapy are too high. Transplant-related mortality in the group of patients who underwent allogeneic SCT after autologous transplantation failure approached 50% in one report.[2]

Relapsed patients BL who were heavily treated and had received high doses of multiagent chemotherapy regimens before receiving HSCT may benefit from a non-myeloablative conditioning chemotherapy regimen

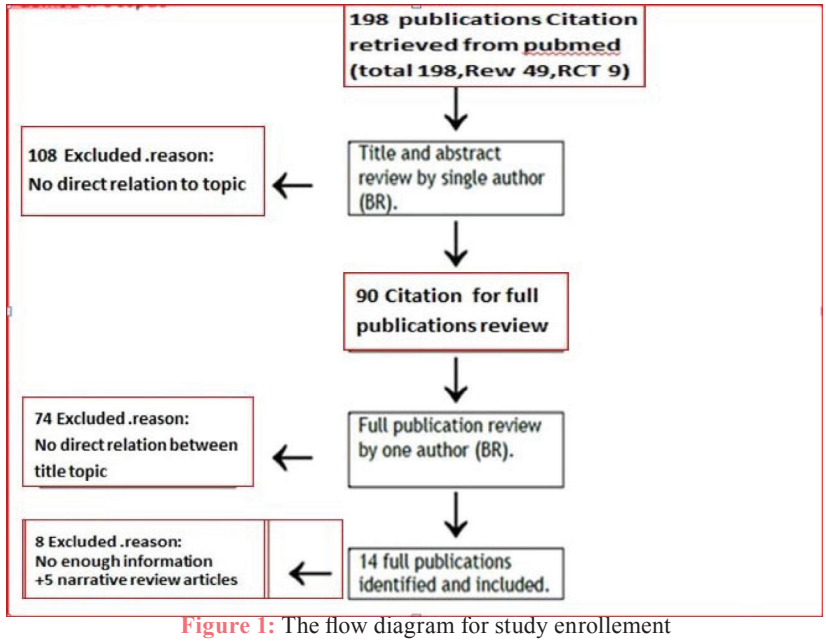

Figure 1: The flow diagram for study enrollement

during allogeneic HSCT.[3,16] One of the major goals in non-myeloablative STC is to establish mixed chimerism with too low toxicity and serious graft-versus-host effects; while retaining graft versus tumor effects which is always associated with conventional conditioning regimens.[17,18] These chimerisms will eventually lead to dominance of a particular population of stem cells, depending upon the balance of donor and recipient T-cell activities.[19]

As a matter of fact, the beneficial effects of graft-versus lymphoma (GVL) in the setting of allogeneic HSCT are not conclusive, particularly when the low response to donor lymphocyte infusion (DLI) in adult acute lymphoblastic leukemia patients is taken into consideration.[20] So, the use of a non-myeloablative regimen permits engraftment of the donor stem cells by creating marrow spacing through the graft-versus-host effect, a phenomenon which usually does not occur by myeloablative regimens or radiation therapy.[21] Although non-myeloablative regimens in other types of NHL are less encouraging due to the high rate of procedure-related complications and also higher risk of relapse. Most patients with lymphoid malignancies undergoing such a procedure have had low or intermediate grade lymphoma while BL is a high grade type of NHL.[22]

Approximately 50% of patients with chemosensitive BL who undergo SCT can be cured; however, a significant number of patients will not proceed to SCT because of early resistance or recurrence.[23]

Conclusion

Both autologous and allogeneic HSCT may improve survival in patients with BL. Autologous HSCT is mainly considered for patients with high-risk features of BL at presentation; however, allo-HSCT with non-myeloablative conditioning regimens are preferred for advanced stages and relapsed/refractory disease.

Conflict of Interest: None declared.

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ORIGINAL ARTICLE

The Efficacy of Single Dose Rasburicase in Prevention or Treatment of Tumor Lysis Syndrome in Children

Samin Alavi[1]*, Maryam Ebadi[2], Sadaf Esteghamati[1], Mohammad Kaji Yazdi[3]

1. Pediatric Congenital Hematologic Disorders Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Department of Pediatrics, Division of Hematology and Oncology, University of Minnesota
3. Department of pediatric Hematology and oncology. Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article History:
Received: 01.02.2016
Accepted: 26.04.2016

Keywords:
Malignancy
Rasburicase
Hyperurecemia
Tumor lysis syndrome

*Corresponding author:
Samin Alavi, MD;
Address: Pediatric congenital hematologic disorders research center, Shahid Beheshti Medical University, Tehran, Iran
Tel: +98 21 22691236
Fax: +98 21 22904536
Email: s.alavi@sbmu.ac.ir

ABSTRACT

Background: Tumor lysis syndrome (TLS) is a major metabolic complication in patients with malignancy after initiation of chemotherapy or spontaneously without treatment. The role of Rasburicase (a recombinant urate-oxidase enzyme) in prevention and treatment of TLS has been demonstrated in recent years. We aimed to investigate the efficacy of a single dose of rasburicase in reducing the risk of TLS in children at high risk.

Methods: we conducted a retrospective analysis of 560 children with various malignancies in a single referral center. On the basis of the reference values previously established in our center hyperuricemia and TLS were defined. Tumor lysis syndrome development was the primary outcome. 48 children with a mean age of 7.1 years (range: 3 months to 15.8 years) developed tumor lysis syndrome. The most common malignancies were B-precursor acute lymphoblastic leukemia (ALL) (45%) followed by non-Hodgkin lymphoma (NHL) and Wilms' tumor (each 10.4%), respectively. They received normal saline intravenously at a rate of 4-5 L/m^2/day in 24-48 hours prior to initiating chemotherapy. Plasma samples were drawn to detect uric acid, calcium, phosphate, potassium, creatinine and blood urea nitrogen (BUN) 4 hours before administering a single dose of IV rasburicase (0.2 mg/kg over 30 minute). Laboratory markers were evaluated again 4 and 24 hours after administering rasburicase.

Results: All patients with diagnosis of TLS had significantly decreased uric acid levels following single dose of rasburicase except 1 patient (2.1%) (P<0.001). Mean plasma uric acid concentration before treatment was 10.0±4.2 mg/dL and 4 hours after treatment declined to 2.2±5.5 (P<0.001). Hyperphosphatemia was also detected in 43.7% of these 48 cases which significantly decreased to 16.7% (P=0.012). Plasma uric acid levels remained low one day after treatment. No side effects were detected.

Conclusion: Rasburicase is a safe and highly effective drug in children with hyperuricemia in the setting of malignancy at risk of developing TLS.

Please cite this article as: Alavi S, Ebadi M, Esteghamati S, Kaji Yazdi M. The Efficacy of Single Dose Rasburicase in Prevention or Treatment of Tumor Lysis Syndrome in Children. IJBC 2016; 8(2): 33-37.

Introduction

In the presence of myeloproliferative disorders and hematologic malignancies, nucleic acids, resulting from increase in tumoral cell mass are catabolized. Increase in purine metabolism results in hyperuricemia and tumor lysis syndrome (TLS).[1] Tumor lysis syndrome occurs due to the release of tumor cell contents leading to electrolyte abnormalities including hyperkalemia, hyperphosphatemia, hyperuricemia, and metabolic acidosis.[2] It may result in acute renal failure (ARF) due to the deposit of excessive amounts of uric acid crystals in renal tubules and cause renal failure with consequent negative influence on the disease prognosis.[3] Despite careful management of metabolic disturbances in order

to decrease the likelihood of developing ARF, it is still observed in 25% of pediatric patients with advanced Burkitt lymphoma and type B ALL.[4,5]

Rasburicase (Elitek®) is a recombinant urate-oxidase enzyme produced by a genetically modified Saccharomyces cerevisiae strain[6] which can be used in both prevention and rapid management of hyperuricemia. The superiority of Rasburicase to other medications including allopurinol in both prophylaxis and treatment of TLS has been reported in several studies.[1,7,8] An advantage of rasburicase over allopurinol is that by inhibiting urate-oxidase, rather than xanthine oxidase, xanthine will not accumulate, hence preventing xanthine nephropathy.[8] By comparing two groups of pediatric patients who received comparable chemotherapy regimens, 2.6% of patients in rasburicase group required dialysis vs. 16% in the allopurinol group.[9] Rasburicase has been the focus of attention especially for pediatric oncologists as an effective factor in the prevention of TLS, nonetheless no study has evaluated its efficacy in our country.

Herein, the authors aimed to study the effects of single dose rasburicase on pediatric patients with malignancies who developped TLS in a referral pediatric center from Iran.

Patients and Methods

In this cross-sectional study, all children (<18 years old) with malignancy in a period of 10 years, presenting to our center were analyzed for the development of TLS. TLS was defined as serum uric acid level higher than 7.5 mg/dL or serum creatinine or lactate dehydrogenase (LDH) level two-folds higher than the upper limit of normal range. Rasburicase was prescribed for patients with evidence of TLS without any history of atopia, asthma or glucose 6-phosphate dehydrogenase (G6PD) deficiency , since rasburicase is contraindicated in these patients.[2] In addition, patients who were previously treated with rasburicase, Uricozyme or allopurinol within the previous 7 days were not included.

48 out of 560 patients had developed TLS. Intravenous normal saline (4-5 liters/m^2/day) was initiated 24-48 hours before starting chemotherapy. Four hours before administering rasburicase, blood samples were drawn and serum levels of uric acid, LDH, calcium, phosphorus, potassium, creatinine as well as leukocyte count were measured. chemotherapy was initiated 4-24 hours after the first dose of rasburicase (i.e., all patients received rasburicase before or during the first cycle of chemotherapy). A single dose rasburicase was administered intravenously (0.2 mg/kg in 30 minutes). Serum uric acid levels were measured 4 and 24 hours after using rasburicase.[4] Also, calcium, phosphorus, potassium, creatinine and BUN serum levels were measured once more after rasburicase administration. A checklist was designed which included various items including age, sex, initial diagnosis, laboratory assays, and any side effects attributed to rasburicase. Mean and standard deviation (±SD) were used to express continuous data and frequency (percentage) for categorical data. The efficacy of rasburicase in decreasing serum levels of assayed markers was tested by repeated measure analysis with a confidence level of 95%. A P value of 0.05 was considered statistically significant.

Primary endpoint was regarded as the development of TLS, either laboratory or clinical TLS, as defined by Cairo and Bishop[10]; briefly, the diagnosis of laboratory TLS was made when 2 or more abnormal laboratory test results were detected 3 days prior to or 7 days after starting chemotherapy including:

uric acid >7.5 mg/dL or 25% increase from baseline; Potassium >6 mmol/L or 25% increase from baseline; Phosphorous >4.5 mg/dL or 25% increase from baseline; Calcium >7 mg/dL or 25% decrease from baseline.

Clinical TLS was described as the presence of laboratory TLS combined with one clinical sign including creatinine> 1.5 times upper normal limit; cardiac arrhythmia; sudden death and seizure.[2] Secondary outcome was described as adverse events especially acute kidney injury Significant reduction in serum uric acid (<6.5 mg/dl) and creatinine was also evaluated as the secondary outcome. Complete physical examination and toxicity assessment were performed at 4 and 24 h after receiving rasburicase.

Parents were informed about the study protocol and written informed consent was obtained. The study protocol was approved by the ethics committee of Shaheed Beheshti university of medical sciences and was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.[11]

Results

Twenty eight (58.3%) girls and 20 (41.7%) boys with a mean age of 7.1 (±4.5) years (range: 3 months-15.8 years) with various malignancies developed TLS (table 1). 3

Table 1: Frequency distribution of malignancies diagnosed in 48 pediatric patients treated by rasburicase

	Frequency	Percentage
B-precursor ALL (acute lymphoblastic leukemia)	22	45.8%
Non-Hodgkin lymphoma	5	10.4%
Wilms' tumor	5	10.4%
Acute myeloblastic leukemia	4	8.3%
Neuroblastoma	3	6.3%
Juvenile myelomonocytic leukemia	3	6.3%
Mature B-cell ALL	2	4.2%
T-cell ALL	1	2.1%
Germ cell tumor	1	2.1%
rhabdomyosarcoma	1	2.1%
Adrenal carcinoma	1	2.1%

(6.25%) children had renal failure at baseline. Table 2 shows the baseline characteristics of the patients before administering rasburicase.

Secondary Outcome

A total of 97.91% of patients with TLS responded to treatment with rasburicase (normalization of uric acid levels). All laboratory markers improved both 4 h and 24 h after rasburicase therapy; changes in uric acid, BUN, Phosphorus and calcium were significant, whereas creatinine and potassium improved only slightly without a statistically significant difference (table 3). However, the number of patients with significant improvement in laboratory markers was only significant in terms of hyperurecemia which decreased from 48 patients to 1 patient. Mean±SD uric acid level was initially 10±4.2 mg/dL which significantly decreased to 2.2±5.5 after 4 hours (P<0.001). Serum uric acid level remained low after 24 hours and its maximum level was 21 mg/dL; nonetheless, hyperuricemia recurred in 4 children including a 7-year-old female with B-precursor ALL and a 2-year-old girl with acute myelogenous leukemia (AML). These patients received a second injection of rasburicase, leading to correction of hyperuricemia. The other patient who suffered hyperuricemia after 24 hours included a 12-year-old boy with mature B-cell ALL, requiring a second administration of rasburicase. The fourth patient was a 3-month-old girl with B-precursor ALL who required rasburicase for 4 times to reach a normal uric acid level.

The number of patients with other abnormal laboratory markers also decreased, yet the difference was not significant (table 4). As shown in tables 3 and 4, all patients had hyperuricemia and 3 (6.25%) had renal failure at baseline which decreased to 2 patients after rasburicase therapy. No side effect including nausea, vomiting, fever, headache, abdominal pain, constipation, diarrhea, mucositis or rash was reported in the patients.

Discussion

Herein, the efficacy and safety of rasburicase in children

Table 2: Baseline characteristics of 48 pediatric patients with malignancies before administering rasburicase are depicted

	B-precursor ALL (N=22)	NHL (N=5)	Wilms' tumor (N=5)	AML (N=4)	Others (N=12)	Total (N=48)
Age, year	7.7 (±5)	11.2 (±2.6)	5.4 (±0.8)	4.1 (±3.5)	6.1 (±4.1)	7.1 (±4.5)
Gender, male	8	2	3	1	6	20
Leukocyte count, $\times 10^9$	54.7 (±66.7)	8.7 (±3.8)	11.1 (±2.9)	34.2 (±20.3)	48.1 (±56.3)	42.7 (±56.1)
Hemoglobin, gr/dL	9.5 (±2.8)	9.7 (±2.2)	10.3 (±2.0)	8.8 (±1.3)	8.7 (±1.8)	9.3 (±2.3)
Platelet count, $\times 10^9$	86.0 (±63.5)	348.6 (±249.6)	363.3 (±4.1)	139 (±15.7)	171.9 (±204)	164 (±170.5)
Uric acid, mg/dL/N*	9.5 (±3.0)/22	10.9 (±2.7)/5	10.4 (±1.2)/5	8.8 (±1.3)/4	10.9 (±7.1)/12	10 (±4.2)/48
BUN, mg/dL/N*	18.8 (±11.7)/5	13.4 (±2.2)/0	10.6 (±5.8)/0	11.0 (±5.5)/0	24.4 (±28.3)/3	18.0 (±16.4)/8
Cretinine, mg/dL/N*	0.7 (±0.4)/1	0.7 (±0.2)/0	0.6 (±0.4)/0	0.5 (±0.1)/0	1.1 (±1.4)/2	0.8 (±0.8)/3
Calcium, mg/dL /N*	9.0 (±1.4)/21	9.6 (±1.0)/5	8.8 (±0.7)/5	9.5 (±0.8)/4	8.6 (±1.3)/11	9.0 (±1.2)/46
Phosphorus, mg/dL/N*	4.6 (±1.9)/10	4.2 (±0.6)/1	3.8 (±0.8)/1	4.8 (±2.0)/3	4.7 (±2.0)/6	4.5 (±1.7)/21
Potassium, mg/dL/N*	4.1 (±0.7)/0	4.0 (±0.4)/0	5.0 (±1.5)/1	4.6 (±0.6)/0	4.2 (±0.8)/0	4.2 (±0.8)/1

N* presents number of patients with abnormal level in each malignancy category
All data are presented as mean (±standard deviation) except for gender which is frequency.

Table 3: Comparison of uric acid, creatinine, BUN, calcium, phosphorus, and potassium serum values at baseline, 4 hours and 24 hours after using rasburicase in 48 pediatric patients with malignancies

	Baseline	4 hours	24 hours	P value
Uric acid, mg/dL	10 (±4.2)	2.2 (±2.5)	2.1 (±3.2)	<0.001
BUN, mg/dL	18 (±16.4)	15.1 (±16)	14.7 (±15.9)	0.043
Creatinine, mg/dL	0.8 ±(±0.8)	0.7 (±0.5)	0.7 (±0.8)	0.221
Calcium, mg/dL	9 (±1.2)	8.8 (±9.4)	8.5 (±0.85)	0.079
Phosphorus, mg/dL	4.5 (±1.7)	4.2 (±1.3)	3.8 (±0.9)	0.007
Potassium, mg/dL	4.2 (±0.8)	4.1 (±0.9)	4 (±0.8)	0.486

P values were obtained applying Friedman test and repeated measure analysis

Table 4: Comparison of the frequency of patients with abnormal laboratory values at baseline, 4 hours and 24 hours after administration of rasburicase

	Baseline	4 hours	24 hours	P value
Hyperuricemia	48 (100%)	1 (2.1%)	1 (2.1%)	<0.001
Elevated BUN	8 (16.7%)	5 (10.4%)	7 (14.6%)	0.861
Elevated creatinine	3 (6.25%)	2 (4.2%)	2 (4.2%)	0.861
Hypercalcemia	46 (95.8%)	48 (100%)	43 (89.6%)	0.058
Hyperphosphatemia	21 (43.75%)	18 (37.5%)	8 (16.7%)	0.012
Hyperkalemia	1 (1.2%)	1 (1.2%)	1 (1.2%)	1

P values were calculated by Pearson chi-squared test

with tumor lysis syndrome was investigated in a single pediatric oncology center in Tehran, Iran. Rasburiucase was found to effectively decrease hyperuricemia, and hyperphosphatemia, but not other electrolyte abnormalities. In addition, it significantly decreased the number of patients with hyperphosphatemia after 24 hours ($P<0.05$), but not other abnormalities. Response rate was 97.91% (47/48) in this study which is in the same line with the 93% response rate observed in a meta analysis on prospective observational studies.[12] However, the number of patients with significant improvement in laboratory markers was only significant in terms of hyperurecemia which decreased from 48 patients to 1 patient. Previously some studies have pointed to high baseline uric acid levels and white blood cell counts as determinants of poor response rate.

TLS mostly develops in patients with NHL, ALL and AML,[13] accordingly most patients in this study had ALL and NHL. It is well described in the literature that hyperurecemia is the most important factor in the development of TLS, therefore, the cardinal purpose of applying rasburicase is to decrease uric acid levels followed by TLS prevention.

Rasburicase is known as a safe and effective urolytic agent for the management of malignancy-associated hyperuricemia in patients suffering from leukemia or lymphoma including those with hyperleukocytosis.[14-16] Introduction of rasburicase as an effective medication in preventing chemotherapy-associated hyperuricemia and TLS has led to studying this agent in different patient populations. Most studies on pediatric patients have demonstrated promising results.[16] Moreover, its superiority over other agents has been described. Goldman et al.[1] compared allopurinol with rasburicase (0.2 mg/kg) in 52 children with leukemia or lymphoma at high risk for TLS. At the end of the trial, mean serum uric acid level was lower in the rasburicase group (7.1 mg/dL) vs. allopurinol group (7.8 mg/dl), indicating the greater efficacy of rasburicase. In addition, uric acid decline was found to be more rapid in the rasburicase group; it declined significantly in 86% of patients after 4h of administration. They concluded that rasburicase is an effective alternative to allopurinol in patients with leukemia or lymphoma undergoing chemotherapy. In another study[15] the usefulness of rasburicase (0.15 or 0.2 mg/kg) in 131 children or adolescents with recently diagnosed leukemia or lymphoma was assessed for 5-7 days. Similar to our findings, a rapid decline in uric acid level was observed in all patients. The authors increased the dose to 0.2 mg/kg, since hyperuricemia was not corrected in some patients and therefore an additional 0.2 mg/kg dose of rasburicase was administered in these patients. In addition, uric acid can increase after the first 24-hour of starting chemotherapy, hence close monitoring of serum uric acid level seems crucial. Likewise in the present study, hyperuricemia recurred in 8.33% (4/48) of patients after the first dose. Three of these patients, a 7-year-old female with B-precursor ALL and a 2-year-old girl with acute myelogenous leukemia (AML) and a 12-year-old male with B-cell ALL, accomplished normal serum uric acid levels after the second injection after 24 h. Nonetheless, the fourth patient, 3-month-old girl with B-precursor ALL, underwent 4 consequent injections to reach a normal uric acid level.

Since TLS is observed 6-72 h after initiation of therapy, 2 sets of evaluation was performed 4-24 h after initiation of rasburicase in this study in accordance with the FDA guidelines.[17] Also, the dosage which has been recommended by the FDA for children is 0.15 - 0.2 mg/kg once daily for maximum period of 5 days.[17] Therefore, a single dose of 0.2 mg/kg was used in this study.

Rasburicase is usually well tolerated; however, serious side effects may occur such as anaphylaxis, rash, hemolysis, and mehemoglobinemia. Fortunately these serious adverse events are rare and only occur in less than 1% of patients.[17] In the current study, no major or minor side effect was observed. In addition to significant decrease in uric acid level, serum phosphorus as well as BUN level decreased significantly. Shin et al.[18] also reported similar findings regarding significant decrease in phosphorus level after administering rasburicase in pediatric patients. Hyperphosphatemia is frequently observed after chemotherapy due to release from malignant cells. Released phosphate forms a complex with calcium, followed by deposition in kidney tubules with consequent development of kidney injury. In addition to malignant tumoral mass, chemotherapy per se can result in hyperphosphatemia.[19] Before starting rasburicase in this study, almost half of the patients (43.5%) had hyperphosphatemia which significantly decreased to about 17% after 24 hours. Although mean values for BUN decreased significantly after 24 hours, the number of patients with abnormal BUN at baseline (8 cases) did not significantly decrease after 24 hours (7 cases). About hyperkalemia, we could not conclude a significant finding as there was only one patient with hyperkalemia and after 24 hours there was still one patient with hyperkalemia. The same applied to serum creatinine level as there were 3 patients with abnormally elevated levels of creatinine which decreased to 2 patients after 24 hours.

Conclusion

Although rasburicase is widely used in developed countries for prophylaxis against chemotherapy-associated hyperuricemia, the experience with this medication in our country is limited. Rasburicase was found to be an effective and safe medication in the management of hyperuricemia, hence the authors recommend its usage in pediatric patients with malignancies at risk for TLS and hyperuricemia.

Conflict of Interest: None declared.

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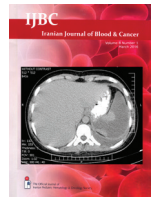
IJBC 2016; 8(2): 38-42

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir



ORIGINAL ARTICLE

Fava Bean Ingestion: the Most Important Risk Factor of Hemolysis in G6PD Deficiency in Iran

Zohreh Kavehmansh*, Atieh Arab, Hassan Abolghasemi, Saman Mohazzab Torabi

Baqiyatallah University of Medical Sciences, Pediatric Department, Tehran, Iran

ARTICLE INFO

Article History:
Received: 17.12.2015
Accepted: 20.03.2016

Keywords:
Fava bean
G6PD deficiency
Hemolysis
Jaundice
Drugs

*Corresponding author:
Zohreh Kavehmansh, MD;
Address: Baqiyatallah Hospital, Sheikh-Bahaei St, Mollasadra Ave, Tehran, Iran
Tel: +98 21 81263716
Fax: +98 21 88055752
Email: z_kaveh@hotmail.com

ABSTRACT

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most known enzyme defects in Iran with various genetic mutations. We aimed to study the predisposing factors of hemolysis in children with G6PD deficiency.
Methods: This study was done during 2007-2012 in two referral centers of Mofid Children's Hospital and Baqiyatallah Hospital, Tehran, Iran. The hospital records of the patients were fully reviewed and questionnaires for each patient were filled for the date of admission, initial symptoms, initial laboratory results, family history and history of any drug consumption, infection or fava bean ingestion.
Results: Medical records of 192 children with mean age of 4.2 years (1 month to 14 years) were extracted. 68.2% of the cases were male. Hemolytic crises were significantly more common in spring which is the peak time for fava bean consumption and occurred more frequently in those with a family history of G6PD deficiency especially in females. The most common initial symptoms were jaundice (71%), dark color urine (49%), fever (34.4%), and pallor (24.5%), followed by abdominal pain (16.7%). Fava bean intake (93%) was the first etiological agent triggering hemolysis followed by infectious agents and drug consumption. Initial hemoglobin level was significantly lower in male patients.
Conclusion: Regarding the high prevalence of G6PD deficiency in Iran, we should emphasize on education of parents and physicians about the disease and prevention of fava bean ingestion in people with G6PD deficiency.

Please cite this article as: Kavehmansh Z, Arab A, Abolghasemi H, Mohazzab Torabi S. Fava Bean Ingestion: the Most Important Risk Factor of Hemolysis in G6PD Deficiency in Iran. IJBC 2016; 8(2): 38-42.

Introduction

G6PD deficiency affects more than 400 million people worldwide. It is highly prevalent in Africa, Asia, and especially in Mediterranean countries.[1] Iran is one of the countries with the highest prevalence of G6PD deficiency according to the World Health Organization (WHO) reports.[2] The prevalence of the disease is reported to be 6.7% in Iran. It seems although neonatal G6PD screening is being practiced in Iran since 2010, the level of education and knowledge of physicians and parents about the nature of the disease and predisposing factors for hemolysis is still essential.[2] Gene frequency for the disease is different from 2.1% in Lebanon[3] to 3.6% in Thailand,[4] 5.1% in Indonesia,[5] and 15.3% in Nigeria.[6] The disease is inherited as an X-linked recessive trait, but the spectrum of the enzyme activity and clinical manifestations are greatly diverse in different populations.[7-9] The most common clinical presentations of people affected with G6PD deficiency are neonatal jaundice and acute hemolytic anemia (favism); while chronic non-spherocytic hemolytic anemia is an uncommon presentation, could be more frequent in geographical areas in which G6PD deficiency is prevalent.[2] Nausea, headache, abdominal pain, chills and fever are the most reported symptoms in acute hemolysis of G6PD deficiency.[10] Prolonged jaundice and Kernicterus may be the other complication of the disease which can cause irreversible effects in the neonates.[6] Hemolysis can in turn cause renal failure or

thrombosis as an ultimate risk. All these presentations could impose heavy economical burden on the health system which is avoidable by early neonatal screening of the disease.

Hemolysis is known to be triggered by various environmental factors; the severity of hemolysis is directly related to the degree of enzyme deficiency. Fava bean ingestion is the most common precipitating factor for hemolysis in G6PD deficient populations.[11,12] Infections such as hand-foot-mouth disease, enteroviruses,[13] hepatitis A,[14,15] typhoid fever,[16] and pneumonia[17] also trigger hemolysis in G6PD deficient persons. Consumption of some antibiotics,[18,19] anti-malarial agents,[19] Aspirin,[20] and sulfonamides,[21] also induce hemolysis in these patients.

Overall 1.4 out of 10,000 patients with G6PD deficiency are affected by severe hemolysis, half of which are preventable.[22] WHO recommends neonatal routine screening of G6PD in those countries with higher prevalence than 3-5% of the population.[21,23] This mass screening is being practiced since 2010 in Iran. In this study we investigated the precipitating factors of acute hemolytic attack in patients with G6PD who were admitted to two hospitals, Mofid Children's Hospital and Baqiyatallah General Hospital, Tehran, Iran.

Patients and Methods

In this cross-sectional study we reviewed hospital records of all 1 month to 14 years old patients with G6PD deficiency and acute hemolysis admitted to Mofid Children's and Baqiyatallah Hospitals during 2007 to 2012. The study was approved by the Research Ethics Committee of Baqiyatallah University of Medical Sciences, Tehran, Iran.

A questionnaire was designed for every patient to be filled based on their hospital records. The questionnaire included all information about precipitating factors of hemolysis (history of any respiratory or gastrointestinal infection, drug consumption) and clinical signs and symptoms such as icterus, pallor, fever, diarrhea, and dark urine. The season of admission along with any family history of G6PD deficiency or hemolysis was also extracted. Laboratory data such as hemoglobin, total and direct Bilirubin level and G6PD status were also included.

The data gathered from the questionnaires were analyzed using SPSS software, version 18. Data were expressed as means±standard deviations (SD) for quantitative data and percentage for qualitative data. Independent t (or MannWhitney U test for nonparametric amounts) and Pearson's Chi-square (or Fisher's exact test) tests were used as appropriated.

Results

During the study period, records of 192 patients were drawn, consisting of 131(68.2%) boys. The most common signs were jaundice (71.4%), dark urine (49%), fever (34.4%), and pallor (24.5%). Abdominal pain was observed in 16.7% of the patients. Overall 179 (93.2%) patients had a history of fresh or dried fava bean ingestion. Drugs, upper respiratory tract and gastrointestinal infections were the following causes in 12, 9, and 3 patients, respectively. 169 patients had just fava bean exposure; other seven cases had drug consumption along with fava bean eating. One patient had upper respiratory tract infection (URI), one URI with drug consumption and another one had hepatitis and fava bean ingestion. Diabetic ketoacidosis was diagnosed in only one patient with hemolysis. 149 patients out of 179 (83.2%) who had history of fava bean ingestion before their hemolysis attack, reported fava bean ingestion in the past without developing any obvious hemolysis. Eight patients had previous history of hemolysis following fava bean ingestion. Risk factors of hemolysis in the patients are shown in table 1.

Neonatal jaundice was reported in 82 (42.7%) patients. The enzyme activity was reported to be deficient in 41 out of 170 patients tested during the hemolytic attack. The hemolytic episodes mostly occurred in Spring (74.5%), followed by autumn (10.9%), winter (8.9%), and summer (5.7%), respectively.

The initial hemoglobin level was significantly lower in male patients ($P<0.001$); it was higher in those with gastroenteritis and positive family history of favism. Positive family of favism was reported in 69.4% patients. Moreover, 96.5% of the admitted patients received blood transfusion during their admission. The interval between fava bean ingestion and onset of hemolysis was minimally 12 hours and maximally 72 hours (mean: 48 hours).

Discussion

We found that the most common precipitating factor for hemolysis in G6PD deficient children was fava bean ingestion and other factors such as infections and drug exposure played a minor role. In 2007, 6.7% of the world population or 450,000,000 people were affected by G6PD deficiency. It is approved that fava bean ingestion and

Table 1: Risk factors of hemolytic crisis in G6PD deficient patients

Risk Factor		Number of Patients	Percent (%)
Fava bean ingestion		169	88.02
Fava bean and Drug exposure		7	3.64
Fava bean and URI		1	0.52
Fava bean and Hepatitis		1	0.52
Fava Bean, Drug exposure and URI		1	0.52
Infections	Gastroenteritis	4	2.08
	URI	5	2.6
Drug exposure		3	1.56
Drug exposure and URI		1	0.52
Total		192	100

infections are the most common factors to precipitate hemolysis in countries where routine neonatal screening programs are not implemented.

Previous reports show African sub-Saharan followed by Middle East countries were the most prevalent areas for G6PD deficiency. Prevalence of the disease in Iran has been previously reported before and is different in various cities from 3.2% to 19.3% of the population.[24,25] A published study from Iran showed that 38 out of 300 students were G6PD deficient, but only 2% of them had history of favism hemolytic crisis.[26] Multiple mutations of G6PD are described in different areas of Iran. Noori Daloii and colleagues reported Mediterranean mutations to be the most prevalent mutation in Golestan province followed by Chatham mutation; and this recent mutation was higher in this state in relation to other provinces of Iran.[27] It seems that Mediterranean mutations are the most important variant of G6PD to precipitate hemolytic crisis in middle East countries.[28] Another report from Kordestan province of Iran also confirms the predominance of Mediterranean and Chatham mutations in this area.[29] High frequency of Mediterranean mutations has also been reported in other countries such as India.[30] In Spain, among 1139 students studied, only 11 were G6PD deficient which two of them had experienced hemolytic crisis of the disease.[31] Shannon and co-workers described 14 black children with G6PD deficiency and hemolytic episode of whom 11 had infections and three had Naphthalene exposure; only 3 had history of fava bean ingestion. Other oxidant agents were not responsible for any of the hemolytic episodes in their study.[32,33] In India the main triggers of hemolysis were viral hepatitis, malaria and bacterial sepsis.[33] In Nigeria 22% of hemolytic crises were reported following respiratory tract infections.[34] Agarwal and colleagues reported 5 patients with hepatitis and G6PD deficiency all of whom had high fever, severe anemia, and reticulocytosis.[35] In Hong Kong herbal drugs followed by fava bean ingestion were mostly responsible in G6PD hemolytic episodes.[22] A report from North Sardina also indicated fava bean ingestion was the most common trigger of hemolytic episode in G6PD deficient patients.[36] Lou and co-workers also reported fava beans to be the main cause of hemolysis in China.[22]

In our study, only 12 patients with G6PD hemolytic episode had evidence of viral infections. This data is different from many other countries. The most important drugs responsible for hemolytic crisis in G6PD deficient people around the world are antimalarial agents.[37-39] In Turkey antimalarial and antipyretics were the most common drugs to be responsible.[40] This was the same in Afghanistan as antimalarial agents and aspirin were reported to be the most common agent.[41] As a result of success of malaria eradication programs in Iran, antimalarial drugs are not among the common triggers of hemolysis in our country. According to a WHO report in 2015, malaria has been on a declining trend in Iran and now is classified in elimination phase.[42] Cefaperazone/sulbactam could be mentioned among antibiotics that can precipitate hemolytic attack in G6PDdeficient patients.[43,44] Since self-medication with antibiotics is common in Iran, these should be kept in mind as an agent to precipitate hemolysis in such patients.[45] Table 2 shows some published risk factors for hemolysis in G6PD deficient patients in the region.

In our study, 82 out of 109 patients had a history of neonatal jaundice. In 109 Nigerian G6PD deficient children studied, 106 of them described neonatal jaundice.[34] Other reports also showed a significant number of neonatal jaundice occurring in G6PD deficient neonates. There is a global emphasis on importance of neonatal G6PD screening especially in those with prolonged jaundice.[46]

Neonatal G6PD screening program is being practiced in Iran since 2010, albeit still increased level of education and knowledge of physicians and parents regarding the nature of the disease and precipitating factors is essential.

Conclusion

The most common agent to induce hemolysis in G6PD deficient patients was fava bean ingestion. This could be severe enough to compromise the vital condition of the patients. According to eradication programs of malaria in our country and rarity of drug-induced hemolytic crises in G6PD deficient patients, increased level of awareness about the nature of hemolysis and importance of fava bean ingestion is advisable.

Conflict of Interest: None declared.

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Table 2: Different studied populations for G6PD deficiency with their precipitating risk factors in the region

Country	Number of study population	Hemolysis risk factor
Jordan[47]	428	Young age, Negative family history, Male
Jordan[48]	258	Fava bean, URI, Drug exposure
Iraq[49]	102	Fava bean, Spring time
Hong Kong[22]	6	Fava bean, URI, Herbal drugs
Thailand[4]	225	Dried Fava bean

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IJBC 2016; 8(2): 43-46

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

ORIGINAL ARTICLE

Epidemiological and Clinicopathological Features of Bladder Cancer: A Report from Kermanshah Province, Iran

Mazaher Ramezani[1], Nima Naderi[1], Afshin Almasi[2], Masoud Sadeghi[3*]

1. Department of *Pathology*, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
2. Department of Biostatistics and Epidemiology, Kermanshah University of Medical Sciences, Kermanshah, Iran
3. Cancer Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

ARTICLE INFO

Article History:
Received: 12.01.2016
Accepted: 28.03.2016

Keywords:
Bladder cancer
Clinical manifestation
Age
Sex
Iran
Pathology
Grading

**Corresponding author:*
Masoud Sadeghi,
Address: Cancer Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
Email: Sadeghi_mbrc@yahoo.com

ABSTRACT

Background: Bladder cancer accounts for about 7% of all cancers among adults in Iran. We aimed to evaluate epidemiological and clinicopathological features of bladder cancer in Kermanshah province, west Iran.

Methods: In a descriptive retrospective study, records of patients with bladder cancer referring to Imam Reza Hospital, Kermanshah city, Iran during 2011-2013 were analyzed. Sex, age, smoking habits, patients' symptoms, *histo*pathology and staging of the tumor *were extracted from the records*. The grading of the tumor was performed according to the Ash grading system.

Results: 220 patients were registered. 179 (81.4%) were patients men. The mean±SD age for patients at diagnosis was 62.5±15.1 years (range: 14-90 years). 71 (43%) patients were smokers. 165 (75%) patients were from rural areas. Hematuria, dysuria, *and frequent or* painful urination were reported *in* 74.5%, 5.5%, and 41.8%, respectively. Transitional cell carcinoma was the most common pathology in 93.2% of the patients. Grade I, II, III and IV tumors were observed in 0.5%, 41.5%, 37% and 21% of the patients, respectively.

Conclusion: Bladder cancer occurs most commonly in the elderly. Bladder cancer in Asia is more common in men compared with Europe and Africa. Since hematuria was the main presenting manifestation of the patients with bladder cancer, elderly patients with hematuria should be referred at the earliest convenience for investigation.

Please cite this article as: Ramezani M, Naderi N, Almasi A, Sadeghi M. Epidemiological and Clinicopathological Features of Bladder Cancer: A Report from Kermanshah Province, Iran. IJBC 2016; 8(2): 43-46.

Introduction

Bladder cancer accounts for 7% of all new cases of cancer in men.[1] Transitional cell carcinoma (TCC) is the most common histological subtype, accounting for approximately 85% of patients.[1] In Iran, bladder cancer accounts for 7.04% of all cancers.[2] Sex, race, and age at diagnosis have a significant impact on mortality from bladder cancer. Tumor grading, staging and histology at presentation also affect the outcome.[3] This cancer is usually discovered in older patients; median age at the time of diagnosis is 69 years for men and 71 years for women according to published data.[2] While men are at a higher risk for developing bladder cancer (80% were male and 20% female),[4] women present with more advanced disease.[5]

A number of etiological factors are associated with the development of bladder cancer. In industrialized countries, cigarette smoking has been recognized as the most important etiological factor.[6] About 94% of bladder carcinomas are composed of transitional cells. Its distinct symptoms are microscopic or macroscopic hematuria and less frequent symptoms include difficulty urinating, frequent urination and therapy-resistant urinary tract infections.[7]

We aimed to evaluate epidemiological and clinicopathological features of bladder cancer in

Kermanshah province, west Iran.

Materials and Methods

In a descriptive retrospective study from 2011 to 2013, records of patients with bladder cancer referred to Emam Reza Hospital, Kermanshah city, Iran were analyzed. Demographic data including age, sex, smoking habits, history of hematuria/painful or difficulty in urination, type of pathology, staging and grading of tumor *were studied for all patients.* Grading of tumors were defined according to the Ash grading system.[8] SPSS software, version 19 was used for data and analysis and figures were plotted in Excel software.

Results

Overall, 220 patients were registered. 179 (81.4%) patients were men. Mean±SD age at diagnosis was 62.5±15.1 years (range: 14-90 years, table 1). The patients were divided into five age groups (table 1). Most patients (60.9%) were >60 years old. 71 (43%) out of 165 patients had a positive history of smoking. 165 (75%) patients were from rural and 55 (25%) patients from urban areas. The most common pathology was TCC with a frequency of 93.2%. Squamous cell carcinoma (SCC) and adenocarcinoma with equal frequency comprised the other pathological subtypes. Of the 205 patients with TCC, one (0.5%) patient, and 85 (41.5%), 76 (37%) and 43 (21%) patients had grade I, II, III and IV tumors, respectively. Frequency of hematuria, dysuria *and frequent or* difficulty in urination *was* 74.5%, 5.5% and 41.8%, respectively. Figure 1 shows the prevalence of patients with grade and sex in bladder cancer. Grade II had the most frequency and Grade I had the lowest in both sex.

Discussion

Bladder cancer is a common malignancy often diagnosed in older adults.[1] The median age at diagnosis in a study was reported to be 69 years for men and 71 years for women.[9] Another research showed 58.4% of the

Table 1: The baseline variables in patients with bladder cancer (n=220)

Variables	n (%)
Age, year	
<30	10 (4.5)
30-40	11 (5)
41-50	20 (9.1)
51-60	45 (20.5)
>60	134 (60.9)
Sex	
Male	179 (81.4)
Female	41 (18.6)
Smoking, n=165	
Yes	71 (43)
No	94 (57)
NA	55
Habitation	
Rural(Village)	165 (75)
Urban(city)	55 (25)
Type of pathology	
TCC	205 (93.2)
SCC	5 (2.3)
Adenocarcinoma	6 (2.7)
Others	4 (1.8)
Grade in TCC patients, n=205	
I	1 (0.5)
II	85 (41.5)
III	76 (37)
IV	43 (21)
Hematuria	
Yes	164 (74.5)
No	56 (25.5)
Dysuria	
Yes	12 (5.5)
No	208 (94.5)
Frequent urination or Difficulty urinating	
Yes	92 (41.8)
No	128 (58.2)

NA: Not available; SCC: Squamous cell carcinoma; TCC: Transitional cell carcinoma

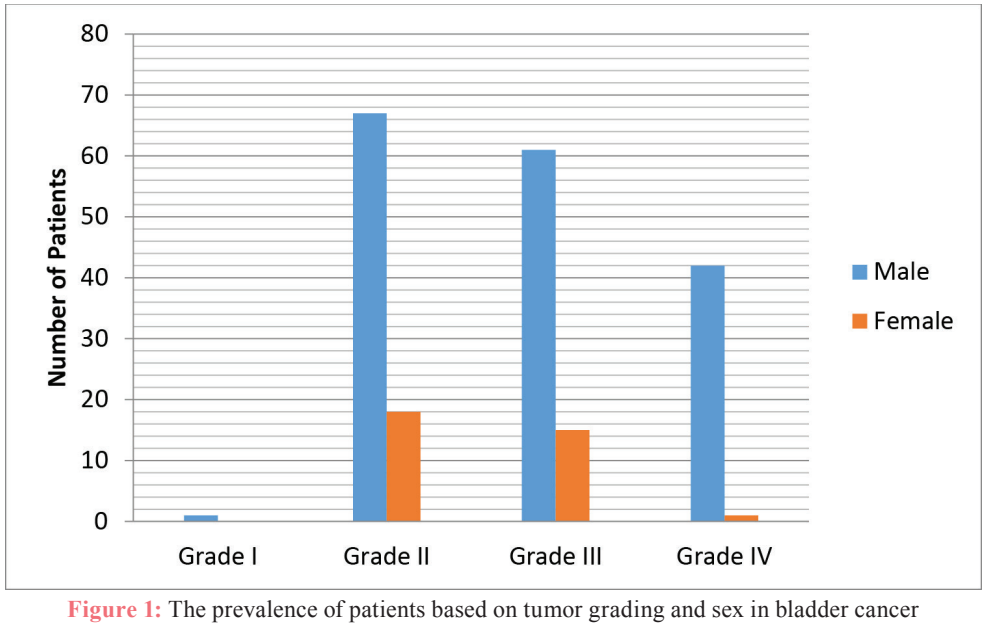

Figure 1: The prevalence of patients based on tumor grading and sex in bladder cancer

patients with bladder cancer were older than 50 years of age.[10] Another study showed that 94.4% of the patients presented with bladder cancer were older than 40 years.[11] The largest proportion of patients (39.8%) with bladder cancer in a study were older than 70 years.[12] In our study 90.5% of patients had age>40 years and 81.4% were older than 50 years. The mean age in our study and other studies, except in two studies, was older than 60 years (table 2). Therefore, the results confirmed that bladder cancer occurs most commonly in the elderly. According to the literature, bladder cancer is more common in men except in a report from Tanzania which was almost equal in both sexes. Therefore, the prevalence of bladder cancer in men in Asia is reported to be higher than Europe and Africa.

Cigarette smoking has been known as an environmental risk factor for bladder cancer.[18] 30%- 50% of patients with bladder cancer had a positive history of cigarette smoking.[19] It accounts for about half of bladder cancers diagnosed among men and about one third of that among women.[20] A study from Iran showed that tobacco and opium use were found in 109 (65.3%) and 44 (34.1%) of the patients, respectively.[12] In our study, 43% of patients were smokers.

We found that 25% of patients with bladder cancer were from urban and 75% from rural areas. In a study, 95.5% of patients with bladder cancer came from urban areas. TCC was the most common variant accounting for 90% of bladder cancer reported in the literature.[21] SCC accounts for only 1% of bladder cancers in England, 3%-7% in the United States and as much as 75% in Egypt.[9] In a study, 97.7% of the patients with bladder cancer had TCC, whereas SCC and adenocarcinoma accounted for 1.04% and 1.25% of the patients, respectively.[11] Frequency of different bladder cancers in a study from Iran was reported with TCC as the most common (95.7%), followed by adenocarcinoma (1.1%) and SCC (0.5%).[12] In our study, frequency of TCC, SCC and adenocarcinoma was 93.2%, 2.3% and 2.7%, respectively. In a study, 44% cases with bladder cancer were Grade II and 29.5% Grade III.[8] Out of 148 patients with noninvasive papillary carcinoma of bladder, 84.5% were high grade (grade III or IV) and 15.5% were low grade (grade I or II).[22] In our study, 58% of the patients was high grade that grade III was 37% and 42 % were low grade that grade II was 41.5%.

Hematuria and dysuria independently are associated with bladder cancer.[23] Bladder cancer is reported to be associated with painless hematuria in 80–85% of the patients.[11] In our study, hematuria, dysuria and *frequent or* difficulty urination were the most common complaints in patients with frequency of 74.5%, 5.5% and 41.8%, respectively. Another study in Iran,[15] reported hematuria, dysuria and difficulty in urination in 49.1%, 12.5% and 9.8%, respectively. Therefore, hematuria is the presenting manifestation of bladder cancer in most patients.[24]

Conclusion

The results confirmed that bladder cancer occurs most commonly in the elderly with male predominance. Hematuria was the most common complaint of patients with bladder cancer; as a result physicians should be alert to refer patients with this symptom for further evaluation particularly in elderly.

Conflict of Interest: None declared.

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Table 2: Age and sex distribution in bladder cancer patients

Reference	Year	Number of patients	Country	Mean age	Range	Male to female ratio
8	1997-2000	495	Pakistan	59	30-87	4:1
10	2000-2010	185	Tanzania	54.3	23-98	0.95:1
11	2001-2008	561	India	60.2	18-90	8.6:1
12	2007-2009	216	South Iran	65.1	-	4.84:1
13	2000-2011	2160	Poland	69.1	11-100	2.96:1
14	1997-2011	31266	Sweden	72	-	2.85:1
15	2010-2011	112	North Iran	68	-	7:1
The present study	2011-2013	220	West Iran	62.5	14-90	4.37:1
16	1973-2003	603	Center Iran	61.9	-	5.8:1
17	1985-2012	190	North Eastern Iran	66.9	-	6.57:1

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IJBC 2016; 8(2): 47-51

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

ORIGINAL ARTICLE

Expression Analysis of Foxo3a Gene in Pediatric Acute Lymphoblastic Leukemia in Southern Iranian Population

Malihe Mirzaei[1,2], Mahboobeh Nasiri[1,2*], Mehran Karimi[3]

1. Department of Biology, Islamic Azad University, Arsanjan Branch, Arsanjan, Iran
2. Young Researchers and Elite Club, Islamic Azad University, Arsanjan Branch, Arsanjan, Iran
3. Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

ARTICLE INFO

Article History:
Received: 09.01.2016
Accepted: 02.04.2016

Keywords:
FoxO3a
Pediatric ALL
Gene expression
PI3K/AKT pathway

**Corresponding author:*
Mahboobeh Nasiri,
Address: Department of Biology, Arsanjan Branch, Islamic Azad University, Arsanjan, Iran
Tel: +98 917 3010601
Email: nasiri@iaua.ac.ir

ABSTRACT

Background: Acute lymphoblastic leukemia (ALL), the most common childhood cancer with a peak incidence in children from 2-5 years old, might be associated with poor prognosis and resistance to therapy in specific cytogenetic backgrounds. FoxO3a, a member of the forkhead class 'O' (FoxO) transcription factors, is a main downstream target of PI3K/AKT pathway which regulates different variety of biological processes and is overactivated in several human cancers. We aimed to evaluate the aberration of the FoxO3a gene in mRNA level in childhood ALL and compare them with healthy controls.
Methods: Real-time quantitative RT-PCR (qRT-PCR) was used to detect FOXO3a expression in 30 new cases of pediatric ALL and 30 age- and sex-matched healthy children as the control group.
Results: the expression level of the FoxO3a gene was significantly lower in ALL patients compared to healthy controls (P<0.0001), while no difference was observed between the two sub-types B- and T-ALL.
Conclusion: Our study suggested that decreased FoxO3a expression may play an important role in the development of pediatric ALL. FoxO3a could be considered as a molecular target of therapy in ALL malignancy.

Please cite this article as: Mirzaei M, Nasiri M, Karimi M. Expression Analysis of Foxo3a Gene in Pediatric Acute Lymphoblastic Leukemia in Southern Iranian Population. IJBC 2016; 8(2): 47-51.

Introduction

Leukemia is a malignancy of hematopoietic cell populations that include diverse and biologically distinct sub-groups.[1] Acute Lymphoblastic Leukemia (ALL) is one of the four major types of leukemia which is common in both children and adolescents; however, it is the most common pediatric malignancy diagnosed in children younger than 20 years.[2,3] Regarding the World Health Organization (WHO) definition, ALL is categorized in B-Lymphoblastic Leukemia (B-ALL) and T-Lymphoblastic Leukemia (T-ALL), originated from B- and T-Lineage lymphoid precursor cells, respectively.[4]

The disease pathogenesis results from blockade at any stages of normal lymphoid differentiation due to uncontrolled proliferation of lymphoid cells.[5] Lack of enough information on the precise origin of the leukemic cells, biological behavior of the hematopoietic primitive cells, mechanisms that damage the earliest steps of the lymphoid development as well as high genetic heterogeneity make ALL a condition full of ambiguity.[6,7]

From genetic point of view, proto-oncogenes and tumor suppressor genes are the most important genes involved in leukemogenesis,[8,9] which their alterations disrupt normal regulatory processes such as self-renewal, proliferation, differentiation and apoptosis in target cells.[10]

FoxOs (Forkhead box, class O) transcription factors function as a tumor suppressor gene and are important for stem cell maintenance.[11] They are key regulators of the cellular differentiation, growth, survival, cell cycle, metabolism, and cellular stress.[12] FoxO1, FoxO3a,

FoxO4 and FoxO6 are four members of the FoxO transcription factor family in humans.[13] FoxO3a expresses in various tissues including B- and T-lineage cells.[12,14] Transcriptionally, FoxO3a activates several target genes such as apoptosis-related genes (Bim, FasL, TRAIL, PUMA) and cell cycle inhibitor genes (P27, P21).[15] FoxO3a is an important target of PI3K/AKT signaling pathway, which is hyperactivated in various type of cancers.[16] Hyperactivation of this pathway in leukemia leads to inactivation of FoxO3a in leukemic cells and eventually tumor growth.[17] This evidence emphasize on FoxO3a as a tumor suppressor role gene. Moreover, overexpression of FoxO3a in B and T cell lines induces cell cycle arrest in G1 phase and triggers apoptosis by induction of the cell cycle inhibitor protein, P27, and pro-apoptotic molecules FasL and Bim, respectively.[14]

So far, few reports have been published concerning the role of FoxO3a in childhood ALL. The expression profile of FoxO3a in childhood ALL has not yet been reported. Thus, we aimed to analyze the mRNA expression level of FoxO3a in children with ALL among the population in southern Iranian.

Patients and Methods

Patient Characteristics and Sample Collection

30 children aged 2-17 years referred to Amir Oncology Hospital, Shiraz, Iran, and diagnosed as new cases of acute lymphoblastic leukemia were included in the study. 30 healthy age- and sex-matched children without a history of any malignancies were enrolled as the control group. The accuracy of the diagnosis was confirmed using immunology and cytogenetic tests as well as monitoring the morphology of the cells. Patients who met the following criteria were excluded; a) age more than 20 years, b) presence of other hematological disorders, history of other malignancies or relapsed ALL, and c) patients under chemotherapy or radiotherapy. The study design was approved by the Ethics Committee of Islamic Azad University, Arsanjan Branch and written informed consent was obtained from the parents of all children who participated in the study.

RNA Extraction and Real-Time PCR Analysis

To determine the expression level of FoxO3a gene, as a candidate gene involving in the pathogenesis of ALL, total RNA from fresh blood samples was isolated using RNX-Plus solution (CinnaGen, Iran) according to the manufacturer's instructions and cDNA was prepared using RevertAid first-strand cDNA synthesis kit (Thermo Scientific Fermentas, USA) following the manufacturer's instructions. All primer pairs used in this study were designed by Allele ID v7.8 software. Primers were specific for mRNA and did not amplify genomic DNA. The primer sequences were as follows: Forward, 5-CGGACAAACGGCTC ACTCT-3 and reverse, 5-GGACCCGCATGAATCG ACTAT-3 for FoxO3a gene; and forward, 5-CCCGAAACGCCGAATATAAT-3 and reverse, 5-CTGGACTGTTCTTCAC TCTTG-3 for TBP gene. The cDNA were subjected to quantitative RT-PCR (qRT-PCR) analysis using a Rotor-Gene Q 2plex HRM Platform real-time PCR system (Corbett Life Science) to evaluate the relative expression levels of FoxO3a and TBP (as an endogenous control gene). Each 15µl reaction volume contained 7.5µl of 2x Evagreen mastermix (Yekta Tajhiz Azma, Iran), 1.25µl of cDNA, and 0.4µl (10pm) of each pair of oligonucleotide primers. All reactions were done in duplicate. The PCR cycling began with an initial step of 95˚C for 15 min followed by 35 cycles of 95˚C for 25 sec, 54˚C for 20 sec and 72˚C for 20 sec; then a melting curve analysis was performed. The threshold cycle (CT) values were determined using Rotor-gene Q sequence detection system. The relative expression levels of the target gene were normalized to that of the endogenous control gene, TBP. The data were analyzed using the comparative threshold cycle ($2^{-\Delta\Delta CT}$) method.

Statistical Analysis

Chi-square test was used to compare the nominal variables among ALL patients (cases) and healthy children (controls). Data were analyzed with GraphPad Prism statistical software (La Jolla, USA) using unpaired t-test to compare the difference in gene expression between cases and controls. P value of <0.05 was considered statistically significant.

Results

Demographic features of ALL cases and controls are shown in table 1. Among them, 9 (30%) patients were diagnosed with T-cell ALL, and the rest (70%) with B-cell precursor ALL. 36.7% of all patients were female, and 63.3% were male. Although there was not a significant difference in frequency of blood groups between the patients and control group, the frequency of blood groups B and O were slightly higher among cases compared to the control group (table 2).

Foxo3a mRNA Expression Analyzed by qRT-PCR

The mRNA level of Foxo3a was measured by qRT-PCR in blood samples derived from ALL patients and

Table 1: Frequency distributions of selected features in ALL cases and controls

Features	Cases (n=30)	Controls (n=30)	P*
Age (range; year)	2-17	1-17	
Age			
≤5	10 (33)[a]	11 (37)	0.79
>5	20 (67)	19 (63)	
Gender			
Male	19 (63)	19 (63)	1
Female	11 (37)	11 (37)	

*Pearson chi-square; [a]Percentage of total within each group/ subgroup.

Table 2: The frequency of blood groups between cases and control

Groups \ Blood types	A^+	A^-	B^+	B^-	O^+	O^-	AB^+
Controls	9 (30)[a]	2 (6.7)	5 (16.7)	0 (0.0)	11 (36.7)	0 (0.0)	3 (10)
Cases	5 (16.7)	1 (3.3)	8 (26.9)	1 (3.3)	12 (40)	1 (3.3)	2 (6.7)
P value[*]	0.72						

[*]Pearson's chi-square; [a]Percentage of total within each group/ subgroup

healthy subjects. The Foxo3a mRNA expression level was significantly lower in ALL patients compared with the control group (P<0.0001). Quantitative RT-PCR showed more than 3-fold downregulation of Foxo3a gene (figure 1).

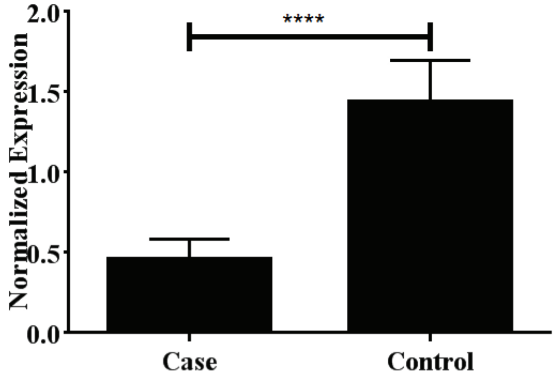

Figure 1: Real-time quantitative RT-PCR analysis of Foxo3a expression in blood samples from ALL patients and controls. The relative mRNA expression of Foxo3a was significantly lower in ALL patients compared with the healthy controls (****P<0.0001).

Furthermore, we analyzed the mRNA expression level of Foxo3a in 21 B-ALL patients compared with 9 T-ALL patients. Results showed more reduction in the FoxO3a expression, but this difference was not statistically significant between the two groups (P=0.23) (figure 2).

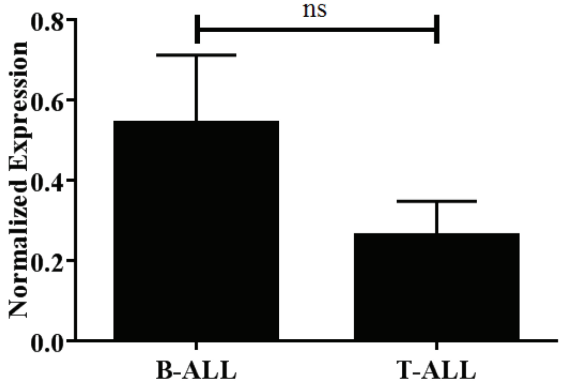

Figure 2: Real-time quantitative RT-PCR analysis of Foxo3a expression in blood samples from B-ALL and T-ALL patients. The relative mRNA expression of Foxo3a showed no significant difference between these two groups (P=0.23).

Discussion

ALL accounts for about 78% of all childhood leukemias.[18] Poor prognosis and resistance toward treatment are the key characteristics which represent some cases of ALL as an incurable cancer.[19] Poor prognosis for ALL reflects in part the lack of knowledge about the tumor basic biology. Present study for the first time, best of our knowledge, demonstrates a new molecule that its aberrant expression plays an important role in ALL pathogenesis among children. Decrease in mRNA level of the FoxO3a gene, as shown in our study confirmed the role of this transcription factor as a tumor suppressor gene in pathogenesis of the pediatric ALL. The result of our study was similar to those for breast, ovarian, prostate and gastric cancers.[13,20-22] In all these studies, it has been shown that overexpression of FoxO3a inhibits cell proliferation and then prevents tumor progression.

It has been demonstrated that PI3k/AKT signaling pathway is a central circuit in pathogenesis of acute leukemia.[23] Constitutive activation of this pathway has been demonstrated as a key pathogenic mechanism involved in AML development.[24] Similar to AML, PI3K/AKT activation is frequently found in B-ALL; however, its alterations is predominant in T-ALL in comparison with other leukemias.[25,26] One of the most favorable downstream effects of the activated PI3K/AKT pathway includes inactivation of FoxO3a through phosphorylation and restoration of this transcription factor.[27] Here, we also suggest the PI3k/AKT signaling pathway as a molecular mechanism which controls cell growth, apoptosis, development and progression of ALL via downregulation of FoxO3a.

One of the previous studies on the chemoresistance of T-ALL cells have shown the cytoplasmic localization of FoxO3a; therefore these cells inactivate FoxO3a in order to escape TRAIL and Noxa-induced apoptosis.[17] FoxO3a deficient mice showed reduced number of Pre-B cells and re-circulating B cells in bone marrow and peripheral blood, so FoxO3a makes a unique contribution to B cell development.[28] Conditional deletion of FoxO3a in mice affects lymphoproliferation and finally widespread organ inflammation. Mice with conditional deletion of FoxO1, FoxO3a and FoxO4 showed abnormalities in lymphoid development resulting in a long term defect in repopulation activity of the bone marrow stem cells.[12,29,30]

In summary, the current study provided information, for the first time, on essential role of FoxO3a in development of ALL disease. Understanding the precise role of FoxO3a in ALL will not only increase our knowledge of the biology of this malignancy but its upregulation may also allow development of a novel therapeutic strategy.

Acknowledgement

The authors appreciate the assistance of Dr. Majid Yavarian for technical and academic assistance. We

also thank Mohammad Moghadam for monitoring the laboratory procedures. The data was provided from the thesis of Ms. M. Mirzaei, MSc student of Molecular Genetics in Islamic Azad University, Arsanjan Branch.

Conflict of Interest: None declared.

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Erratum:

Volume 7, Number 4, Supplement: The International Congress of Challenges in Pediatric Hematology and Oncology (CPHO)

One of the authors of the published abstract entitled "Prevalence and Related Factors of iron deficiency Anemia in Iranian Children" has been mistakenly ommited from the byline as follows:

Nastaran Norouzi Parashkouh

Affiliation: Department of Nursing (Community Health), Faculty of Nursing and Midwifery Ramsar, Babol University of Medical Sciences, Babol, Iran.

IJBC 2016; 8(2): 52-55

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

ORIGINAL ARTICLE

Preliminary Results of Allogenic Hematopoietic Stem Cell Transplantation of non-M3 Acute Myeloid Leukemia

Farhad Shahi[1], Marziye Ghalamkari[2*], Seyed Reza Safayi[1], Mehrzad Mirzania[1], Mahdi Khatuni[2], Faeze Almasi[2]

1. Department of Hematology and Medical Oncology, Cancer Research Center, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
2. Internal Medicine Resident, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article History:
Received: 20.12.2015
Accepted: 30.02.2016

Keywords:
Prognostic factors
Karnofsky performance status scale
GVHD
2-year overall survival
Non-M3 AML
Allogenic stem cell transplantation
Autologous stem cell transplantation

*Corresponding author:
Marziye Ghalamkari, MD;Address: Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 912 6018502

ABSTRACT

Background: Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) is used as treatment of choice for patients with acute myeloid leukemia (AML). We aimed to evaluate the prognostic factors in 2-year overall survival of patients with non-M3 AML who underwent allogenic HSCT.

Methods: This is a Cross sectional retrospective study. Demographic data and study of variables such as age, sex, complete remission status, Karnofsky performance status scale at baseline and at time of transplantation, occurrence of GVHD (acute and chronic), relapse and 2-year survival were extracted from records of 49 patients who underwent allogenic HSCT from years 2006-2013 at BMT center in Imam Khomeini Hospital. All Autologous SCTs and M3 cases were not included. All data were analyzed with SPSS software. $P<0.05$ was considered as statistically significant.

Results: The overall survival rate was 55% in the patients. There was no significant difference in overall survival between complete remission (CR) 1 and CR2. Relapse rate was 6%. Mean 2-year Karnofsky scale was 93.7. Mean admission time following BMT was 22 days which was significantly related to 2-year performance status ($P=0.02$). Admission complication rate was 22.5% (GVHD 12%). Rate of overall GVHD was 55%, 40% of whom developed chronic GVHD which had a positive effect on 2-year overall survival (OS2).The patient's first performance state (K1) had a significant correlation with 2-year performance state ($P<0.05$) and OS2 ($P<0.05$).

Conclusion: Chronic GVHD and initial Karnofsky performance status scale can be considered as good prognostic factors in patients with AML who undergo allo-HSCT.

Please cite this article as: Shahi F, Ghalamkari M, Safayi SR, Mirzania M, Khatuni M, Almasi F. Preliminary Results of Allogenic Hematopoietic Stem Cell Transplantation of non-M3 Acute Myeloid Leukemia. IJBC 2016; 8(2): 52-55.

Introduction

Acute myeloid leukemia (AML) is a malignant hematological disorder which is caused by clonal expansion of myeloid progenitors. However, chemotherapy is the frontline treatment approach in most hematologic malignancies such as acute lymphoblastic leukemia, is not much efficient in patients with AML.[1] As an alternative and practical method, hematopoietic stem cell transplantation, allogeneic or autologous, has been shown to lead to long-term remissions and cure for patients with AML. Although both approaches are associated with increased survival and improved quality of life,[1,2] the type of donor highly affects the outcome of the patient. Given the high risk of recurrence with autologous hematopoietic stem cell transplantation (HSCT), this method is not curative and progression is

inevitable.[3] In contrast, allogeneic HSCT (allo-HCT) is a potentially useful treatment option for patients with AML because of absence of contaminating tumor cells in the graft and the potential for a GVHD effect.[3,4]Although allo-HSCT improves the outcome of patients with AML, response to the treatment and survival rate varies in these patients. Age of the patient, karyotype, cytogenetic and molecular characteristics of each patient could be considered as prognostic factors.[5] However, the role of some important factors, such as impact of GVHD as a key determinate and performance status of the patients in the context of allo-HSCT have not yet been fully clarified. Therefore, we aimed to evaluate prognostic factors in 2-year overall survival of patients with non-M3 AML who had undergone allo-HSCT.

Patients and Methods

This was a cross-sectional retrospective study in patients who had been diagnosed with AML. The study was performed at the Bone Marrow Transplantation (BMT) center at Imam Khomeini Hospital, Tehran, Iran and was approved by the Hospital's Ethics Committee. The eligible patients were all patients who had been diagnosed with AML according to the World Health Organization classification and had received allo-HSCT during 2006-2013. The patients who had been diagnosed with other malignancies and/or M3-AML or those who had received autologous SCT were excluded from the study.

The patients who received allo-HSCT were fully HLA-matched with their donors. The preparative regimen for all patients was cyclophosphamide 5 mg/kg/d on days 1 and 2 and busulphan 4 mg/kg/d on days 3 to 6. Karnofsky performance status scale was used to evaluate the overall health and quality of life of the patients in initial manifestation of the disease and two years after transplantation. The scoring is a 0 to 100 scoring system in which zero score means the patient is dead and score of 100 means the patient is capable of doing normal activities and no special care is needed.

The description of complete remission (CR) and overall survival (OS) followed the recommended consensus criteria. OS was measured from the transplantation day until the day of event (such as relapse) and was documented.[6] Continuous variables included: donor age, sex, initial clinical sign, interval between initiation of chemotherapy and hybrid cell injection, flowcytometry status, interval between initial diagnosis and treatment and transplantation and the interval between SCT and relapse. Disease-free survival (DFS) rate, 2-year survival rate after allo-HSCT, and the patients' quality of life two years after transplantation were considered as dependent variables.

Categorical variables such as sex and donor type were indicated with counts and percentages. Descriptive statistics (proportions, percentages mean and standard deviation) was used to describe the demographic characteristics and frequency of symptoms. To assess the relationship between the frequency of clinical symptoms or variables listed in the methodology, the Chi-square or Fisher's exact tests were used. Quantitative variables were compared with two tailed Student's t-test. Statistical analyses were performed using the software package of SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

The number of allo-HSCT cases that were registered in the BMT center of Imam Khomeini Hospital during the study period were 49, of which 22 (49.1%) patients were male. 73.5% of the patients were younger than 40 years old. The percentage of patients receiving allo-HSCT was increasing during the last years of the study (2010-2013, figure 1).

Most patients (30.6%) were in their fourth decade of life. The youngest patient undergoing SCT was 15 years old and the eldest was 52 years. AML-M2 was the most common type in patients who received allo-HSCT. All patients (98%) except one, received the transplant from a fully-matched sibling donor.

Transplant Outcomes

The rate of 2-year overall survival was 55%. 55% of patients were in first complete remission (CR1), while

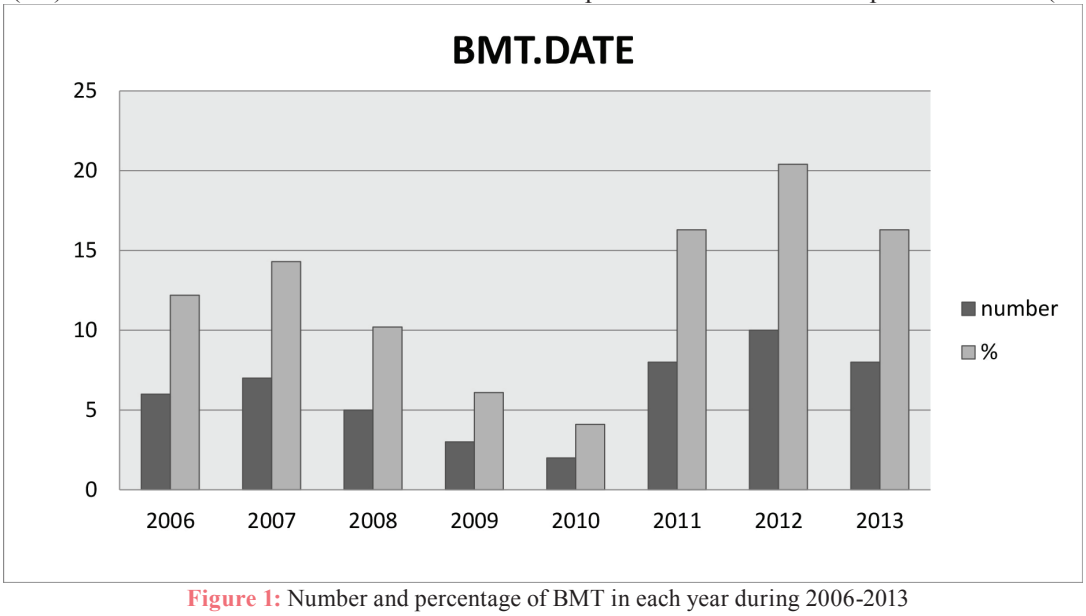

Figure 1: Number and percentage of BMT in each year during 2006-2013

45% received salvage chemotherapy (primary refractory) and were in CR2. There was no significant difference in OS between patients who were in CR1 or CR2. Relapse of disease was recognized in 6% of the patients following HSCT. Mean 2-year Karnofsky scale was 93.7. Mean admission time post BMT was + 22 days which was significantly correlated to 2-year performance status (P=0.02). 22.5% of the patients were admitted due to complications, half of which were related to acute graft versus host disease.

The overall rate of GVHD was 55%. The number of acute GVHD episodes was 15 (7 episodes occurred in one patient). 53% of acute GVHD cases progressed to chronic GVHD. The overall rate of chronic GVHD was 40% which had a positive effect on 2-year OS. The patient's first Karnofsky performance scale (K1) had a significant correlation with 2-year Karnofsky performance scale (P<0.05) and 2-year OS (P<0.05).

Discussion

The present study showed the practicability and usefulness of allo-HSCT in patients with AML. It also confirmed the support of beneficial effects of chronic GVHD and patient's performance status to progression of 2-year overall survival rate. The low relapse rate of patients (6%) can be considered as the main reason to consider allo-HSCT in AML patients who do have the indications to receive transplantation in our institution. Our results also showed that CR1 and CR2 did not affect 2-year overall survival rate. Our results were in contrast to Krauter and colleagues' study showing that a comparable outcome can be achieved when allo-HSCT is successfully performed in CR1, but deferring the transplant to a later time may compromise the survival of the patients.[7]

The incidence of GVHD as a major cause of non-relapse mortality was 55% with chronic GVHD in 40% of the patients. There was significant correlation between chronic GVHD and two-year OS in the patients; the patients with chronic GVHD do experience better outcome. Our results regarding beneficial effects of GVHD on 2-year OS was in contrast to another study showing that the occurrence of GVHD could not necessarily have a beneficial effect on reduction of mortality rate.[8] The inconsistency may be related to differences in patient characteristics enrolled in two studies; the researchers of the mentioned study had surveyed GVHD effect on 2-year survival rate in patients in CR2,[8] while in our study discrimination for CR1 or CR2 was not considered and we analyzed correlation of GVHD with 2-year survival rate in all patients.

Our results indicated that the Karnofsky performance status scale at the beginning of the study had a significant correlation with the corresponding 2-year scale and 2-year OS.

Krauter and colleagues reported age as a determining risk factor of outcome following allo-HSCT;[7] however, most of our patients were younger than 40 years old and this may explain the lack of correlation between age and 2-year survival rate.

Our study was also consistent with other studies that patients with active disease at the beginning of transplantation had a higher rate of relapse.[7,9,10]

Conclusion

Our results showed an acceptable profile for allo-HSCT in treatment of patients with AML, although relapse remains the main problem after allo-HSCT in patients with AML. Identifying the patients at risk before or after transplant would improve the results of allo-HSCT. Our results indicated that occurrence of chronic GVHD and initial Karnofsky performance status scale of the patients can be used as prognostic factors for estimation of 2-year survival rate.

Conflict of Interest: None declared.

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IJBC 2016; 8(2): 56-58

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

Case Report

Recurrent Venous Thromboembolic Events in a Child with Severe Factor X Deficiency

Peyman Eshghi, Mohammad Kajiyazdi, Mohammad Hammoud*

Pediatric Congenital Hematologic Disorders Research Center, Mofid Children Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article History:
Received: 15.01.2016
Accepted: 06.03.2016

Keywords:
Factor X deficiency
Prothrombin time
Partial thromboplastin time
Thromboembolic event

**Corresponding author:*
Mohammad Hammoud, MD;
Address: Mofid Children's Hospital, Dr Shariati Ave, Opposite Hosseinieh Ershad, Tehran, Iran.
Tel: +961 3000647
Email: drmham82@gmail.com

ABSTRACT

Congenital factor X deficiency is a rare autosomal recessive bleeding disorder that presents with variable bleeding tendency and prolonged coagulation tests, prothrombin time, and partial thromboplastin time. Thromboembolic events have not been reported in patients with factor X deficiency yet. Herein, we report a patient with factor X deficiency who had recurrent venous thromboembolic events.

Please cite this article as: Eshghi P, Kajiyazdi M, Hammoud M. Recurrent Venous Thromboembolic Events in a Child with Severe Factor X Deficiency. IJBC 2016; 8(2): 56-58.

Introduction

Factor X deficiency is a rare autosomal recessive severe bleeding disorder with a worldwide incidence of 1:500,000-1000,000.[1] According to last report of the World Federation of Hemophilia's annual global survey 2014, 1655 cases of factor X deficiency has reported to date.[2] A wide spectrum of clinical symptoms ranging from minor bleeding, excessive bleeding after trauma or surgery and rarely hemarthrosis to life threatening bleeding has been described in the affected person.[3] The diagnosis of factor X deficiency is based on coagulation tests prothrombin time (PT), activated partial thromboplastin time (aPTT), Dilute Russell's viper venom time and chromogenic assay to measure the coagulant activity of factor X (FX:C) and then if possible by immunoassay to detect plasma Factor X antigen levels (FX:Ag).[2] No thromboembolic event has ever been reported in patients without any history of previous treatment with coagulant products. Here we report a patient with severe factor X deficiency presenting with recurrent venous thromboembolic events.

Case Report

An 8-year-old boy who was a known case of severe factor X deficiency was referred to Mofid Children's Hospital with abdominal pain. The diagnosis of factor X deficiency was made at 3 years of age based on bruising in the extremities which was confirmed by coagulation test assays and factor X level of 0.3% was documented in the patient. Further molecular studies at the age of 6 showed a homozygous p.Gly363Ser mutation at the encoding gene for factor X which is located on chromosome 13 (13q34). He was admitted with impression of appendicitis or intra-abdominal bleeding for evaluation of abdominal pain. Physical examination was unremarkable for guarding or rebound tenderness. Radiological findings were not conclusive. After a couple of hours the patient's abdominal pain subsided and he complained of a localized severe inguinal pain. Doppler ultrasound study showed

a decrease in the venous blood flow of common femoral vein along with a large thrombosis extending from it to the right saphenous vein. During the past two months he had not received any plasma or prothrombin complex concentrate products. A comprehensive laboratory assessment did not show any significant finding except for a protein S activity of 32% which was not clinically significant. The patient was scheduled to receive simultaneously FFP and low molecular weight heparin (LMWH). After clinical and radiological improvement, the patient continued the treatment for about 45 days. Two weeks after the cessation of FFP and LMWH the patient referred to our clinic with a severe pain in left upper extremity which Doppler ultrasound again showed a thrombosis in the left brachial vein. The patient was treated again with FFP and LMWH for one month until clinical and radiological findings were improved.

Two years later he also developed a deep venous thrombosis in the left femoral vein which was treated as before. Continuous therapy with FFP and LMWH or vitamin K antagonists was not considered for the patient due to the risk of bleeding regarding the underlying disease and lack of monitoring facilities. Currently, the patient is not receiving any product or anticoagulation treatments and is being observed for on-demand therapy.

Discussion

Factor X deficiency is a rare bleeding disorder inherited as autosomal recessive which was first described in two patients independently. The factor is also known as Stuart-Prower factor. It is a Vitamin K dependent glycoprotein which is changed to its active form as a serine protease both by factor VII and calcium, with tissue thromboplastin in the extrinsic pathway. Factor Xa is also involved in the macromolecular complex formation with its cofactor Va, tissue phopholipid and calcium to convert prothrombin to thrombin.[3] Acquired deficiencies of factor X is reported most commonly with plasma cell dyscrasia and primary amyloidosis; however, there are few reports of acquired deficiency with anticoagulant treatment, liver dysfunction, treatment with phenytoin and viral infections.[4] The factor X production is encoded by a gene of 27 kb located on chromosome 13.[3] Patients with severe FX defects tend to be the most seriously affected comparing with other rare bleeding disorders.[2] Although the more severely affected patients (FX activity <1%) present early in life with umbilical or central nervous system (CNS) bleeding, the bleeding tendency may appear at any age. Patients with severe deficiencies commonly experience hemarthrosis and hematomas.[3,5] However, gastrointestinal, umbilical cord bleeding, hematuria and CNS bleedings may also occur.[5,6]

There are some reports of thrombotic events in other bleeding disorders such as hemophilia A and B, VWD, factor VII deficiency, hypofibrinogenemia and dysfibrinogenemia, although thrombotic events in factor X and FII deficiency except in the setting of over-dosage of plasma products have not ever been reported. Girolam and colleagues explained the clinical significance of the lack of arterial or venous thrombosis in patients with congenital prothrombin or FX deficiency and they have concluded that lack of any thrombotic events in these two conditions is the rationale for use of direct thrombin or factor X inhibitors in the prophylaxis and/or therapy of thrombotic manifestations.[7] We did not find any explanation for recurrent venous thromboembolic events in our case despite performing extensive assays. Our patient had a mild decrease in Protein S activity which might be due to heterozygosity for protein S deficiency. Although, sustained deep venous thrombosis, superficial thrombophlebitis or pulmonary embolism were reported in 74, 72, and 38 percent of 71 protein S deficient persons from 12 Deutch pedigrees, the mean age of the first thrombotic event was 28 years with a range between 15 and 68 years; 56 percent of the episodes were apparently spontaneous and the remainder were precipitated by an identifiable factor.[8] Our patient was also heterozygote for MTHFR A1298C mutation, but the homocysteine levels in two occasions were normal. However, false negative and normal homocysteine level has been reported in MTHFR mutation.[9] It may be related to high folate diets or increased activity of bypassing enzyme pathways. Since there was no other underlying disorder in our patient, co-inheritance of heterozygote Protein S deficiency and mutated MTHFR A1298C may be the sole explanation for thrombotic events in our patient.

The most problematic issue in this case was the management of thrombotic events since LMWH was not expected to be efficient in severe factor X deficient patient and warfarin could not be monitored by PT in this case of severe deficiency of a common pathway factor. We used a combination of antithrombotic along with FFP simultaneously until the clinical response ensued.

Conclusion

Thrombotic events is reported rarely in a variety of bleeding disorders, but in severe deficiency of factor X has not been reported yet. Its occurrence need to be evaluated for possible co-inheritance of thrombophilic disorders. There is also a challenge in management of these thrombotic events in terms of treatment and its monitoring.

Conflict of Interest: None declared.

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Iranian Journal of Blood & Cancer

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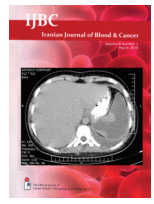

Letter to Editor

Positive Indirect Coomb's Test as an Indicator of Bombay Phenotype of O-group Donors

Shivali Sehgal*, Priti Chatterjee, Swati Bhardwaj, Chintamani Pathak

Department of Pathology, Lady Hardinge Medical College, New Delhi

ARTICLE INFO

Article History:
Received: 03.02.2016
Accepted: 28.04.2016

**Corresponding author:*
Shivali Sehgal, MD;
Address: Department of Pathology, Lady Hardinge Medical College, New Delhi, 110001
Email: shivalisehgal@gmail.com

Please cite this article as: Sehgal S, Chatterjee P, Bhardwaj S, Pathak C. Positive Indirect Coomb's Test as an Indicator of Bombay Phenotype of O-group Donors. IJBC 2016; 8(2): 59-60.

Dear Editor

Bombay blood group, first reported by Bhende et al.,[1] is the rarest of the rare blood groups. It is usually confined to Southeast Asian countries.[2] It is characterized by absence of the H antigen on the surface of the red cells and presence of anti H, anti A and anti B in the serum.

A 22-year-old man came to be our blood bank as a first time replacement donor. Routine blood group was performed and was found to be O positive. Indirect Coombs test (ICT), which is done as a routine in all donors, was strongly positive (4+). Further workup for positive ICT was done by performing the Biorad ID–DiaCell I-II-III Asia 3-cell panel. A 4+ reaction was seen in all the tubes. The 11 cell panel (Biorad ID- DiaPanel) which was performed next also gave a 4+ reaction with all the 11 cell types. Autocontrol, however was negative ruling out autoimmune antibodies as a cause of positive ICT. Reverse grouping with pooled A cells, B cells and O cells was performed showing agglutination (4+ reaction) in all the tubes. This showed presence of an antibody in the serum of the donor which reacted with antigens present on A, B and O cells. Such an antigen is the H antigen, thus the possible antibody in the donor was anti-H. This antibody is found in the very rare "Bombay blood group" which has no H antigen on the red cells and a naturally occurring anti-H antibody in the serum. Presence of anti-H in the serum was responsible for the 4+ reaction with all the cells types in the 3-cell and 11-cell panels since these cell types are of the O group and have H antigen on the red cells. The Bombay blood group was confirmed by lack of agglutination with anti H antisera. Thus positive ICT was the first indicator of the Bombay phenotype. The donor's family could not be tested for Bombay phenotype since he was a replacement donor and was lost to follow-up.

The probability of finding a person with Bombay phenotype is 1 in 250,000 people.[3] India has the highest number of people with Bombay phenotype (1 in 7,600 people).[3] This may be due to the higher number of consanguineous marriages in India.

During routine cell grouping, Bombay blood group is categorized as O group because there is no reaction with anti A or anti B antibodies. It is usually during cross matching that one notes incompatibility with all other O group blood samples. Blood from Bombay blood group donors is precious and should be reserved for patients with the Bombay blood group phenotype. Cryopreservation of blood units of this rare blood group may make blood readily available for such recipients. It is also important to screen family members of persons with this blood group since it is very likely than one or more relatives have the blood group. Such individuals should be counseled to become voluntary donors and register themselves in blood banks, so that if need arises, they can be contacted.

Conflict of Interest: None declared.

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IJBC 2016; 8(2): 61-62

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

PHOTO CLINIC

Leukemia Cutis in a Child with Acute Lymphoblastic Leukemia at Diagnosis and Relapse

Ahmad Mohammadi Ashiani*, Farhad Madani

Pediatric Congenital Hematologic Disorders Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article History:
Received: 15.03.2016
Accepted: 01.05.2016

**Corresponding author:*
Ahmad Mohammadi Ashiani, MD;
Pediatric Congenital Hematologic Disorders Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email: ahmadm_59@yahoo.com

Please cite this article as: Mohammadi Ashiani A, Madani F. Leukemia Cutis in a Child with Acute Lymphoblastic Leukemia at Diagnosis and Relapse. IJBC 2016; 8(2): 61-62.

A 9-year-old boy who was diagnosed with acute lymphoblastic leukemia (ALL) at the age of five developed a combined testicular and bone marrow relapse after 4 years while he was off therapy for one year.

At initial diagnosis of acute leukemia, physical examination was remarkable for splenomegaly and an ulcerative lesion on his cheek. Immunophenotyping was in favor of Pre-B ALL. Cytogenetic study was positive for t(12,21). He was treated with BFM oriented protocol for standard ALL. Chemotherapy was continued for three years. At relapse, physical examination disclosed splenomegaly and unilateral testicular enlargement. Bone marrow aspiration was also indicative of relapse. He was scheduled to receive protocol for relapsed ALL (ALL-REZ BFM) consisting of repeating chemotherapy courses of R1, R2 and R3. Orchiectomy was performed for the involved testis and he received radiation to the contralateral testis. He was also considered to go through allogenic hematopoietic stem cell transplantation. After receiving two cycles of each course, an ill-defined ulcer with erythematous border was observed on his cheek at the same place of the original ulcer at primary diagnosis (figure 1). Skin biopsy revealed infiltration of lymphoblasts. It was considered as extramedullary relapse while his bone marrow was in morphologic remission at this time and minimal residual disease was reported negative by flowcytometry. This is the first case of ALL in a child who developed LC as an extramedullary site of relapse at second relapse after receiving intensive chemotherapy.

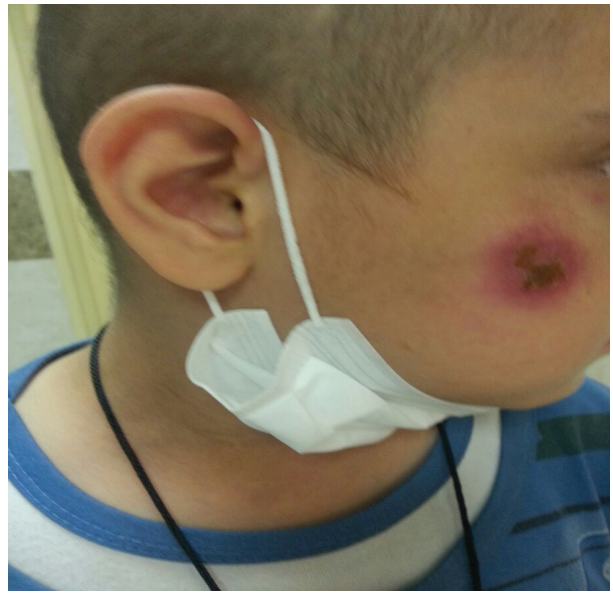

Figure 1: An ill-defined ulcer with erythematous border was observed on the cheek

Leukemia cutis (LC) is defined as infiltration of the skin with lymphoblasts and is an extramedullary manifestation

of leukemia. The cutaneous involvement has a wide spectrum of manifestations ranging from nodules and plaques to rare lesions such as erythematous macules, blisters and ulcers.[1] LC is an uncommon finding in ALL. It typically manifests as red or violaceous papules mainly on the face.[2] Skin is a very rare extramedullary site that can be involved in relapsed cases of leukemia. LC is considered a poor prognostic marker heralding hematologic and bone marrow relapse.[3] Isolated cutaneous relapse has been reported in a 9-year-old girl with AML who was treated successfully with electron beam therapy to the skin lesions.[4]

Conflict of Interest: None declared.

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