Atopy manifestations in pediatric patients with acute lymphoblastic leukemia: correlation assessment with interleukin-4 (IL-4) and IgE level

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common type of cancer in the age range of under 15 years old and accounts for 25–30% of all childhood cancers. Although conventional chemotherapy regimens are used to improve the overall survival rate, it has been associated with some complications, amongst which allergic manifestations with unknown mechanisms are more common.

Methods: Our study compared serum IgE and IL-4 concentration, as a hallmark of allergic responses in pediatric ALL patients before and after 6 months of intensive (high-dose) chemotherapy, to show whether changes in the level of these markers may be associated with atopy. Serum level of IL-4 and IgE was measured using enzyme-linked immunosorbent assay (ELISA) method.

Results: The results showed that the level of IgE and IL-4 increased following chemotherapy in both ALL patients with and without atopy. In addition, post-chemotherapy treatment IgE and IL-4 levels were significantly elevated in patients with atopy compared to those without it. The difference between baseline and post-chemotherapy level of IgE and IL-4 was significantly higher in patients with atopy compared to those without it.

Conclusions: To the best of our knowledge, this is the first study that showed a connection between post-chemotherapy allergic manifestations in pediatric ALL patients and IL-4 and IgE level. Flow cytometry analysis of the T-helper 2 (Th2) lymphocytes and other allergy-related T cell subsets like Tc2 and Th9 as well as the study of the genetic variations in atopy-related genes like IL-4/IL-4R, IL-5, IL-9, IL-13, and high affinity FcεRI IgE receptor and also HLA genes is necessary to clearly define the underlying mechanism responsible for post-chemotherapy hypersensitivity reaction in pediatric ALL patients.

Keywords: Acute lymphoblastic leukemia, Atopy, IL-4, IgE

Background

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer (accounting for about 25–30% of cancers in children under 15 years old) and also the most common type of leukemia (about 80%), characterized by malignant transformation of the lymphoid precursors in the bone marrow [1]. Usually, chemotherapy is used as...
the standard first line treatment for pediatric ALL. The
established treatment protocol includes induction, con-
solidation, and long-term maintenance, along with CNS
prophylaxis given at specified intervals during therapy
[1, 2]. Although chemotherapy has greatly improved the
clinical outcome of patients, the main barrier is post-
chemotherapy adverse events, which potentially affect
the efficacy of treatment [1, 2]. Hypersensitivity is the
major infusion reaction observed after chemotherapy,
which occurs as a result of the immune system activa-
tion against chemotherapeutic agents [3, 4]. However,
the rate of these reactions has been reduced remarkably
by administration of the less immunogenic form of chem-
otherapy drugs [3, 5, 6]. Nevertheless, some patients still
develop hypersensitivity reactions with unknown rea-
son. The underlying mechanism has not been clearly
defined, but production of the allergy-promoting media-
tors by the immune system might be implicated in this
phenomenon.

IL-4 is the most common cytokine produced by T-helper 2 (Th2) lymphocytes and the key cytokine that
regulates Th2 cell polarization [7, 8]. Signaling delivered
through IL-4/IL-4R promotes STAT3 activation followed
by activation of c-Maf and GATA-3 Th2-polarizing tran-
scription factors, which further stimulate Th2 cell dif-
erentiation and IL-5, IL-13 as well as IL-4 production.
Therefore, they potentiate Th2 responses [7, 8]. In addi-
tion, IL-4/IL-4R signaling promotes B cell proliferation
and stimulates immunoglobulin class-switching to IgE
antibody, the major antibody in allergic reactions [7, 8].
Production of these cytokines by Th2 lymphocytes and
other cells accounts for the activation of the mast cells,
asbestos, eosinophils and smooth muscle cell con-
traction as well as stimulation of B cell differentiation
into IgE-producing plasma cells, thus promoting several
allergic reactions including allergic rhinitis, anaphylaxis,
allergic dermatitis, and asthma [7–9]. Until now, there has
not been enough data on whether the hypersensitivity
events in ALL patients are dependent on the IL-4 and IgE
production or not. Therefore, in this study, we aimed to
evaluate the allergic manifestations in pediatric patients
during intensive (high-dose) chemotherapy and its asso-
ciation with change in the serum IgE and IL-4 levels dur-
ing this period.

Methods

Patients’ characteristics and study design

This is a cohort study in which 39 newly diagnosed
untreated pediatric ALL patients who were admitted
from May 2019 to January 2021 in Amir Oncology Hospi-
tal affiliated to Shiraz University of Medical Sciences were
enrolled. All participants had confirmed diagnosis of
ALL (B-ALL/T-ALL) by bone marrow aspiration, biopsy,
and flowcytometry and had received standard risk or
high-risk chemotherapy protocol, which was adjusted by
the age and total white blood cell count at presentation.
All patients experienced chemotherapy drugs including
vincristine, doxorubicin, peg-asparaginase, methotrexate,
cytosar, mercaptopurine, thioguanine, and cyclophos-
phamide during the first 6 months of intensive therapy.
Inclusion criteria were newly diagnosed untreated ALL
patients with negative history of atopy among them or
their first-degree relatives. Exclusion criteria were his-
tory of previous treatment with chemotherapy agents for
any reasons and/or previous history of any rheumato-
logic or any chronic diseases, which need regular medi-
cal treatment as well as congenital or acquired cellular or
humoral immunodeficiency disorders.

Patients were followed through the first 6 months of
intensive (high-dose) chemotherapy for any allergic man-
ifestations including allergic rhinitis (AR), upper airway
hypersensitivity reaction, asthma, urticaria, and eczema.
Accordingly, among the included patients, those who
showed allergic symptoms at the end of 6 months high-
dose chemotherapy were considered as the atopy (+) group. The remaining patients who did not present aller-
gic symptoms were known as the atopy (-) group. The
laboratory data including white blood cell (WBC) and
platelet (Plt) count, percentage of the neutrophils, lym-
phocytes, and eosinophils as well as serum hemoglobin
(Hb) level were measured in all patients at diagnosis and
after 6 months of therapy.

Sample collection

Five milliliters of the peripheral blood were collected
prior to chemotherapy onset and before maintenance
therapy (about 6 months after intensive chemotherapy
treatment). The serum specimens were isolated from the
samples by centrifugation (Sigma-Aldrich, USA) of blood
samples at 3000 rpm for 5 min; then, they were kept at
-80 °C refrigerator until use.

Quantification of serum IgE

Serum IgE was measured using enzyme-linked immuno-
sorbent assay (ELISA) method (AccuBind®, Monobind Inc., Lake Forest, USA). The sensitivity of the kit was
0.1424 U/ml. The concentration of IgE antibody in
unknown samples was calculated based on the standard
curve. OD value at 450 nm was measured for all samples
by spectrophotometer (BioTek Epoch, UK).

Quantification of serum IL-4 cytokine

Serum IL-4 was measured by enzyme-linked immuno-
sorbent assay (ELISA) method (Invitrogen, USA), accord-
ing to the manufacturer’s instruction. The sensitivity of
the kit was <2 pg/ml with assay range (7.8–500 pg/mL)
and the specificity was 3% (Intra-assay) and 4.5% (Interassay). The OD value at 450 nm was measured for all samples by spectrophotometer (BioTek Epoch, UK). The concentration of IL-4 cytokine in the serum of patients was calculated according to the standard curve.

Statistical analysis
All data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 23. Descriptive data were presented as mean ± standard deviation (SD) and percentages. Comparison of qualitative and quantitative variables was performed by Chi-square test and Student t-test between the two groups of patients, respectively. Comparison of the serum level of IgE and IL-4 at baseline and 6 months after treatment was done by Paired t-test in each group. Pearson correlation coefficient was calculated for the relationship of quantitative variables. P-value less than 0.05 was considered statistically significant.

Results
This study included 39 newly diagnosed pediatric ALL patients; 23 patients (59%) developed post-chemotherapy atopic manifestations. The mean age of the patients was 8.7 ± 3.49 (range 4–15 years) and 9.19 ± 3.97 (range 2–15 years) in the atopy (+) and atopy (-) groups, respectively. The male/female ratio was 14/9 and 9/7 in the atopy (+) and atopy (-) groups, respectively. The male/female ratio was 14/9 and 9/7 in the atopy (+) and atopy (-) groups, respectively. The baseline and 6-month value of serum IgE was calculated and compared in the atopy (+) as well as atopy (-) groups. The results showed that the level of serum IgE significantly increased in the atopy (+) group in comparison to its baseline level in the atopy (-) patients (51.2 ± 35.22 vs. 21.86 ± 7.75, respectively; *P < 0.001) (Fig. 1). Furthermore, the concentration of the serum IL-4 of the atopy (+) group was significantly raised 6 months after treatment compared to the baseline level (20.84 ± 5.86 vs. 7.75 ± 20.84, respectively; *P < 0.001) (Fig. 1). Moreover, the concentration of the serum IL-4 of the atopy (+) group was significantly raised 6 months after treatment compared to the baseline level (20.84 ± 5.86 vs. 7.75 ± 20.84, respectively; *P < 0.001) (Fig. 1). Consistent with the serum IgE, the post-chemotherapy level of IL-4 was significantly higher in the atopy (+) patients compared to the atopy (-) ones (51.2 ± 35.22 vs. 21.86 ± 7.75; *P = 0.001).

Comparison of the change in the serum IgE and IL-4 between the atopy (+) and atopy (-) groups
The change in the concentration of serum IgE and IL-4 was calculated by subtraction of their initial value from their post-chemotherapy value and considered as “difference” or “change” in the expression of serum IgE and IL-4 level during this time. Then, the difference in the concentration of the serum IgE and IL-4 was compared

### Table 1 Comparison of demographic, clinical and laboratory characteristics of patients with (atopy+) and without atopy (atopy-)

| Parameters | Atopy (+) (n = 23) | Atopy (-) (n = 16) | P-value |
|------------|-------------------|-------------------|--------|
| Age (year) | 8.7 ± 3.49 | 9.19 ± 3.97 | 0.685 |
| Sex (m/f)  | 14/9 | 9/7 | > 0.999 |
| Laboratory data | | | |
| WBC count (× 10^3) | 4.14 ± 1.9 | 6.87 ± 4.34 | 0.109 |
| Neutrophil (%) | 9.38 ± 9.14 | 18.42 ± 16.53 | 0.083 |
| Lymphocyte (%) | 82.09 ± 12.27 | 69.42 ± 18.69 | 0.38 |
| Eosinophils (%) | 1.21 ± 0.53 | 1.45 ± 0.68 | 0.288 |
| Plt (× 10^3) | 151.23 ± 36.25 | 150.64 ± 71.05 | 0.974 |
| Hb (g/dL) | 8.59 ± 1.61 | 9.13 ± 1.74 | 0.354 |
| Baseline IgE (IU/ml) | 28.55 ± 20.51 | 21.05 ± 12.85 | 0.375 |
| Baseline IL-4 (pg/ml) | 21.86 ± 7.75 | 20.84 ± 5.86 | 0.657 |

### Clinical characteristics

| ALL type | B-ALL | T-ALL | Unknown |
|----------|-------|-------|---------|
| n | 16 | 9 | 2 |

| Cytogenetic | t(10, 14) | t(12, 21) | t(1, 19) | t(4, 11) | t(8, 14) | t(9, 22) | trisomy 4, 10, 17 | t(1, 19) | t(12, 21) | t(10, 14) | t(4, 11) | t(8, 14) | t(9, 22) | trisomy 4, 10, 17 | t(1, 19) | t(12, 21) | t(10, 14) |
|-------------|---------|---------|---------|---------|---------|---------|-------------|---------|---------|---------|---------|---------|---------|-------------|---------|---------|---------|
| n | 2 | 5 | 3 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 3 | 3 | 2 | 2 | |

Data are presented as mean ± SD
between the atopy (+) and atopy (-) patients. The results demonstrated that the serum IgE level significantly changed in the atopy (+) compared to the atopy (-) patients following chemotherapy (420.82 ± 124.03 vs. 132.89 ± 81.62, respectively; *P < 0.001) (Fig. 2). Similarly, the difference of serum IL-4 was significantly higher in the atopy (+) patients compared to the atopy (-) group (29.33 ± 5.58 vs. 2.16 ± 1.71, respectively; *P = 0.001) (Fig. 2). No correlation was observed between the changes in the serum IgE and IL-4 levels among the atopy (+) as well as atopy (-) patients (P > 0.05).

**Change in the serum IgE and IL-4 level and demographic and laboratory data**

The difference in the level of IgE and IL-4 was compared between males and females. Accordingly, the serum IgE and IL-4 alteration did not significantly differ between males and females in patients with and without atopy (P > 0.05). No positive correlation was observed between the difference in IgE and IL-4 level and age of patients with and without atopy (P > 0.05). In addition, the IgE and IL-4 change did not correlate with laboratory data including WBC and platelet count, percentage of the neutrophils, lymphocytes,

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**Fig. 1** The baseline and 6-month level of IgE (A) and IL-4 (B) in the atopy (+) and atopy (-) pediatric ALL patients. The graph is created by GraphPad Prism 8. Data are presented as mean ± SD. P < 0.05 is considered as statistically significance. Atopy (+): patients with atopy, Atopy (-): patients without atopy.
and eosinophils as well as Hb level in patients with and without atopy ($P > 0.05$).

**Discussion**

For many decades, conventional chemotherapy regimens, which is used to improve the overall survival rate in children with ALL, has been connected to different adverse events, amongst which allergic manifestations have gotten more attention [3, 10]. Even though the effector mechanisms are not clearly identified, IgE antibody (antibody-dependent allergic reactions) and other allergy-related mediators including IL-4 cytokine might be involved in the pathogenesis of chemotherapy-related allergic manifestations. In this study, serum IgE and IL-4 levels were evaluated at baseline and after 6 months of chemotherapy as a hallmark of post-chemotherapy allergic susceptibility mediators to show whether changes in their level is associated with hypersensitivity presentations in pediatric ALL patients during high-dose intensive chemotherapy.

Our results showed that the amount of IgE and IL-4 increased after 6 months in both ALL patients with and without atopy compared to the baseline level in each related group, but 6-month post-chemotherapy level of both IgE and IL-4 was significantly higher in the atopy (+) compared to the atopy (-) group. In addition, changes in the IgE and IL-4 levels after 6 months were significantly higher in the atopy (+) compared to the atopy (-) group.

Post-chemotherapy hypersensitivity reactions are the commonly observed feature of cancer patients. It is not clear whether changes in the IL-4 and IgE levels in our study are secondary to immune dysregulation in these patients or they are a general reaction against chemotherapy drugs. Although both atopy (+) and atopy (-) ALL patients actually received the same main treatment protocol, the reasons of why atopy is limited to some patients are unknown.

Obviously, genetic factors like special variants of the IL-4, IL-4R, and IL-13 genes may have a prominent role in development of allergy [11–14]; therefore, their contribution should be carefully noticed. Consistent with this, studies showed that cytokine variants including TNF-α 308 A → G, IL-13 and IL-4RA as well as genetic variation in IgE receptor were associated with predisposition to drug-induced allergy [15, 16]. Interestingly, recent studies revealed that in addition to IgE-mediated drug-induced allergic reactions, differences in major histocompatibility complex (MHC) molecules are the main contributor of T cell-dependent drug-induced allergic manifestations [16]. The types of drugs as well as repeated exposure to chemotherapeutic agents are other factors that have a
fundamental role in antibody-mediated allergic reaction and thus, should be taken into account in patients’ management [3, 17].

Therefore, the study of polymorphism in the atopy-related genes including IL-4/IL-4R, IL-5, IL-9, IL-13, IgE receptor, and genetic variations in HLA molecules should not be underestimated and might provide additional data on the exact role of these factors in the development of allergic manifestations in ALL patients. In addition, analysis of IL-4 and IgE concentration at different time points post-chemotherapy especially when patients entered the maintenance phase is required to specify the role of chemotherapy in this phenomenon.

T-helper 2 (Th2) subtypes of CD4\(^+\) T cells are a subgroup of the lymphocytes which contribute mainly to allergic reactions and immune responses against parasites and helminthes by production of the cytokines IL-4, IL-5, IL-9 and IL-13 that promote B cell proliferation and immunoglobulin class-switching to immunoglobulin E (IgE) [7]. Data on Th2 responses and its related cytokines is very limited in ALL patients and their mechanism of action is poorly understood in these patients. In a study by Zhang et al. on the IL-4-producing CD4\(^+\) (Th2) and CD8\(^+\) (Tc2) subpopulations, it was demonstrated that the Th1/Th2 and Tc1/Tc2 ratios were significantly decreased in the peripheral blood T cells of ALL patients (n = 30) compared to the healthy controls, suggesting the dysregulated differentiation of Th2 and Tc2 in these patients [18]. Also, Horacek et al. reported a higher IL-4 level in the serum samples of newly diagnosed ALL patients compared to the healthy controls [19]. Stachel et al. showed the increased expression of IL-4 mRNA in the bone marrow of 49 pediatric patients with B cell precursor ALL with late relapse proposing that ALL leukemic cells mediate a shift toward Th2 responses and, thus, influence the relapse risk [20]. Consistent with this, Cardoso et al. revealed that IL-4 positively stimulated the proliferation and growth of T-cell ALL cells by activating mTOR signaling which affects the disease outcome [21]. However, Pérez-Figueroa showed a polarized Th1 cytokine profile (IFN-γ and IL-12) in children with ALL (newly diagnosed) while the level of Th2 cytokines (IL-4 and IL-13) were similar compared to the healthy control group [22].

Our study confirmed that both atopy (-) and atopy (+) ALL patients developed higher IgE and IL-4 (albeit with the higher extent for atopy (+) patients) after chemotherapy compared to their corresponding baseline level. Although the reason for this finding is not clear, it could be assumed that the increase in the IL-4 and IgE production in both atopy (+) and atopy (-) patients might be the result of the dysregulated Th2 responses in these ALL patients. In addition to Th2 lymphocytes, CD8\(^+\) T cells as well as cells of the innate immune system including the mast cells, eosinophils, basophils, NKT cells and, innate lymphoid cells are also responsible for IL-4 production and IgE class-switching [9, 23]. Accordingly, flow cytometry analysis of Th2 lymphocytes at baseline and after 6 months of chemotherapy can be highly informative and may be necessary to clarify whether Th2 lymphocytes are implicated in the elevation of IL-4 and IgE production in ALL patients and consequently, post-chemotherapy allergic manifestations in the atopy (+) group. In line with this scenario, it should be noticed that comparison of the frequency of other CD4\(^+\) subsets that are linked to the allergic diseases like Th9 cells between the atopy (-) and atopy (+) patients could clearly define the underlying mechanisms responsible for allergic symptoms in atopy (+) patients. Moreover, mast cells are another compartment of the immune system, which are known as a key driver along with IgE in pathophysiology of allergic reaction [24, 25]. Engagement of FcεRI IgE receptor on the surface of mast cells leads in to mast cell activation and degranulation and thereby, release of inflammatory mediators like histamine, prostaglandins, leukotrienes, cytokines/chemokines, and neutral proteases (including chymase and tryptase) which promote allergic responses [24, 25]. It is tempting that the difference in the mast cell characteristics might be responsible for allergic manifestation in some ALL patients post chemotherapy. This assumption needs to be verified by more studies.

The small number of ALL patients is another limitation of our study that should be taken into account. Accordingly, multi-center studies with higher number of ALL patients could be helpful for better understanding the biological role of IL-4 and IgE as well as other allergy-related mediators in the pathogenesis of post-chemotherapy atopy in ALL patients.

**Conclusion**

It is the first time that the higher concentration of IL-4 and IgE has been shown to be associated with post-chemotherapy allergic manifestations in ALL patients. Larger number of ALL patients along with the specific analysis of the Th2 lymphocytes and also other allergy-related subsets like mast cells, Tc2 and Th9 cells is necessary to clarify the role of these cells in post-chemotherapy hypersensitivity reactions in pediatric ALL patients. In addition, study of the genetic variation in IL-4/IL-4R, IL-5, IL-9, IL-13 cytokines, high affinity FcεRI IgE receptor as well as HLA genes and also the evaluation of the level of the cytokines at different time points post-chemotherapy could assist in delineating specifically the underlying mechanism responsible for atopic manifestation post-chemotherapy in some ALL patients.
the corresponding author on reasonable request. The datasets used and/or analyzed during the current study are available from Availability of data and materials

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Authors’ contributions

Zekavar OR. contributed to the study design, analysis, interpretation of data and writing paper; Nikpendar E. contributed to sample collection and performing the research; Haghpahang S. contributed to analysis, interpretation of data and critical revision of the manuscript; Shokrogoz N. and Dehghani SJ. contributed to performing the research; Arandi N. contributed to the study design, analysis and interpretation of data, performing the research, drafting and critical revision of the manuscript. The author(s) read and approved the final manuscript. Authors’ contributions

ethical approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by Ethics Committee of Shiraz University of Medical Sciences with ethics code of IR.SUMS.MED.REC.1398.665. Written informed consent was obtained from all participants or their legal guardians. Consent for publication

Not applicable. Competing interests

The authors declared that they have no conflict of interest. Author details

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