Original Article *Iran J Ped Hematol Oncol. 2025, Vol 15, No 3, 543-553*

Overexpression of the IL-33/ST2 in Pediatric Acute Lymphoblastic Leukemia: Evaluation of the Effects of a Treatment Program

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Received: 11 November 2024 **Accepted:** 24 May 2025

Abstract

Background: The study focuses on B-acute lymphoblastic leukemia (B-ALL), a common childhood blood cancer marked by an overproduction of B lymphocytes. It explores the role of cytokine expression changes, particularly Interleukin-33 (IL-33), which has both anti- and pro-tumor effects. The research assesses the expression of IL-33 and its receptor, suppression of tumorigenicity 2 (ST2), in B-ALL patients before and after chemotherapy treatment.

Materials and Methods: In this quasi-experimental investigation, peripheral blood specimens were taken from 33 newly-diagnosed/untreated ALL patients. An induction chemotherapy course was administered to ALL patients for 30 days following diagnosis. Blood samples were taken again after the completion of induction chemotherapy. 30 healthy individuals with matched age and gender were also recruited as a control group. Serum IL-33 quantities were assessed using the ELISA method. Total RNA was extracted from peripheral blood samples, and the gene expression of IL33 and ST2 was measured using real-time PCR.

Results: In B-ALL patients, the pre-treatment serum IL-33 concentrations (33.89 ± 4.38 Pg/mL) were substantially greater than the healthy group (20.66 ± 2.20 Pg/mL, $P<0.02$). Pre-treatment expression of IL-33 and ST2 mRNA (1.79 ± 0.18 and 1.42 ± 0.18) was also significantly higher than those in the healthy group (1.00 ± 0.10 and 1.00 ± 0.09; $P<0.001$ and $P<0.05$, respectively). After chemotherapy, serum IL-33 concentrations (22.40 ± 2.60 Pg/mL) and mRNA expression of IL-33 (0.91 ± 0.15) were significantly reduced compared to pre-treatment levels ($P<0.04$ and $P<0.001$, respectively). There were no notable differences in serum IL-33 levels or mRNA expression of IL-33 and ST2 between controls and treated patients ($P<0.61$, $P<0.63$, and $P<0.48$, respectively).

Conclusion: Greater expression of IL-33 and ST2 was observed in B-ALL patients, which were decreased at the end of a therapy course.

Keywords: Acute lymphocytic leukemia, Interlukine-33, Suppression

Introduction

Acute lymphoblastic leukemia (ALL) is characterized by the massive expansion of immature B or T lymphocytes in the bone marrow and other lymphoid organs (1, 2). Globally, the number of ALL cases has grown from 49100 patients in 1990 to 64200 cases in 2017 (3). ALL is the most prevalent kind of childhood cancer, affecting approximately 25% of cases (4). Children aged 1–4 years have the greatest incidence, which subsequently drops remarkably during childhood (5-14 years), adolescence, and early adulthood (15-39 years), with the minimum incidence happening at 25-45 years (5). The development of ALL has been linked to a variety of genetic abnormalities as well as

[DOI: 10.18502/ijpho.v15i3.18920]

environmental variables (5). Cytogenetic analysis in an Iranian population revealed that the BCR-ABL fusion gene [t(9;22)] was the most prevalent abnormality in ALL patients (6). Over two to three years, the current ALL therapy comprises four courses: induction, consolidation, intensification, and long-term maintenance (5). Pediatric ALL has a high cure rate of over 80%, but a proportion of patients may face relapse, which highlights the need for innovative treatment strategies such as immunotherapy (2, 7).

Cytokines are low-molecular-weight proteins that are involved in the stimulation of immunological responses to pathogens, immune regulation, and disease pathogenesis (8). The impaired expression of cytokine and/or their receptors, on the other hand, can facilitate the onset and development of some kinds of cancer, including hematopoietic malignancies (9, 10). In hematopoietic cells, cytokines usually promote survival, self-renewal, differentiation, and proliferation. However, interrupted cytokine signaling pathways have been found in all kinds of leukemia, which contribute to cancer development, metastasis, and resistance to treatment (11). Interleukin-33 (IL-33) is liberated into the extracellular region in response to cell injury and operates as an alarmin (12, 13). Although many cell types naturally generate IL-33, it can be induced in various cells, such as macrophages, endothelial cells, fibroblasts, and epithelial cells (14). The c-terminal part of IL-33 binds to a dimeric receptor made up of the specific subunit Suppressor of Tumorigenicity 2 (ST2) and the IL-1R accessory protein (IL-1RAcP). After binding of IL-33 to IL-33R, it recruits adaptor molecule MyD88, subsequently stimulating transcription factors nuclear factor kappa B (NF-κB), activator protein 1 (AP-1) and extracellular signal-regulated kinase (ERK) (14, 15). Suppressor of Tumorigenicity 2 (ST2) that serves as a binding receptor for IL-33 is expressed on various cell types, including natural $CD8^+$ T-, natural killer (NK)-, Th1-, Th2-, and regulatory T (Treg) cells (16). The binding of IL-33 to ST2 enhances Th2 cell differentiation, aiding in the defense against helminth infections and playing a role in allergic disorders (17, 18). Within the tumor microenvironment, IL-33/ST2 signaling induces Treg and Th2 cell-skewed responses, which inhibit anti-tumor immunity, thereby promoting tumor progression (19, 20). It was reported that IL-33 exerts two immunological functions in cancer. It can enhance anti-tumor immune responses by increasing natural killer T (NKT)-, NK-, Th1-, and $CD8^+$ T cell-related activities (15, 21, 22). IL-33 can also have pro-tumorigenesis impacts via reinforcing the Treg-, Th2-, regulatory B (Breg)-, and M2 macrophage-related responses (15, 22, 23). IL-33 is overexpressed in different kinds of malignancies, such as breast, gastric, prostate, and lung cancers (22, 24, 25). There are controversies regarding the IL-33 roles in hematologic malignancies as it can exert pro-tumorigenesis effects in chronic myelogenous leukemia (CML), whilst performing anti-tumorigenesis impacts in the acute myeloid leukemia (AML) (16). A recent study revealed that IL-33 inhibits apoptosis in ALL cells by inducing mitogen-activated protein kinase (MAPK) and AKT-related signaling pathways (26).

Assessment of the IL-33 and ST2 expression can provide new insights into their role in tumorigenesis and their clinical application in the prognosis and treatment process (27). The expression of IL-33 and ST2 in ALL patients, as well as in pre- and post-treatment times, were not sufficiently evaluated. The investigation aimed to assess the expression levels of IL-33 and ST2 in the peripheral blood of newly diagnosed patients with ALL in the

[DOI: 10.18502/ijpho.v15i3.18920]

pre-treatment time and after completion of induction chemotherapy.

Materials and Methods

Subjects

From February 2019 to March 2020, 33 newly diagnosed/untreated ALL patients referred to the Hematology and Oncology unit of Afzalipoor Hospital, affiliated to Kerman University of Medical Sciences, were enrolled in this quasi-experimental investigation. In addition, 30 healthy children matched for gender and age were included as a control group. The sample size was calculated based on the following formula using α=0.05 and β=0.2:

$$n_1 = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \times (\sigma_1^2 + \frac{\sigma_2^2}{k})}{\Delta^2}$$

.

B-ALL patients with a confirmed diagnosis of B-ALL, age <16 years, newly diagnosed (no prior therapy) and consent to participate were enrolled. B-ALL patients who received other chemotherapy programs were excluded from the study. The healthy control group had no history of hematological abnormalities or malignancies, no acute or chronic illnesses, and was not taking any medication. Children with illnesses, including a history of atopic diseases, asthma, allergies, recurrent infections, or suspected immunological disorders, as well as those using any medication, were excluded from the study. Expert oncologists performed the B-ALL diagnosis, according to the WHO criteria, based on the enumeration of cellular markers, such as HLA-DR, CD10, CD19, CD20 and CD22. A blood sample was collected from all patients before initiating treatment.

Follow up after the treatment program

An induction chemotherapy course was then administered during 30 days after diagnosis. Induction chemotherapy is designed to eliminate the burden of malignancy and re-establish normal hematopoiesis to reach complete remission (5). Induction therapy usually consisting a combination of chemotherapy of glucocorticoids (such as Prednisone), L-asparaginase, Vincristine, Anthracycline, Daunorubicin, and Cytarabine (5). Blood samples were collected again at the end of induction chemotherapy. Total RNA was extracted from all blood specimens, and the sera were frozen at −80 °C. The study protocol was also approved by the ethical committee of the Kerman University of Medical Sciences and documented with an ethics code: IR.KMU.REC.1396.2228.

Determination of serum levels of IL-33.

Serum IL-33 quantities were assessed and expressed as Pg/mL using a commercial human IL-33 ELISA kit (R & D, USA) based on the manufacturer's guidelines.

Determination of mRNA expression of IL-33 and ST2

RNX-plus solution (Yektatajhiz, Tehran, Iran) was used to extract total RNA from blood specimens. Electrophoresis on a pretreated agarose gel with a safe stain dye was used to estimate the RNA quality. RNA quantity and purity were estimated by reading its absorption at 260 and 280 nm, as well as calculating the 260/280 ratio with a spectrophotometer. The extracted RNA was treated with DNase I and incubated at 37°C for 30 minutes to remove any DNA contamination. Complementary DNA (cDNA) was generated from the RNA template utilizing a cDNA synthesis kit (Parstous, Iran) containing both random hexamer and oligo (dT) primers. The process of cDNA generation was designed based on the following protocol: 65°C for 5 min, the addition of reverse transcriptase, 25°C for 10 min, 47°C for 60 min, and 70°C for 10 min to finish the reverse transcription. Gene expression analysis of IL33 and ST2 was conducted in a real-time PCR system (Applied Biosystems, USA) using a green SYBR master mix (Parstous, Iran), mixed with 2 µL proper primers (Table I) and 200 ng of cDNA.

The amplification program was conducted as follows: a primary denaturation at 95°C

[DOI: 10.18502/ijpho.v15i3.18920]

for 10 min, followed by 50 cycles of 95°C for 15 seconds and 56 °C for 20 seconds, and a final extension at 60°C for 1 minute. The β-actin was utilized as a housekeeping gene to normalize the produced signals from the target genes. The expression amounts of the IL33 and ST2 genes were assessed by $2^{-\Delta\Delta CT}$ formula and normalized relative to the mRNA amounts of β-actin.

Statistical analysis

Results were presented as mean ± SEM. ANOVA, *Student t,* and chi-square tests were used for statistical comparisons. The *P* values below 0.05 were deemed meaningful. Data analysis was performed with SPSS software, version 22 (SPSS Inc, Chicago, IL, USA).

Results

The mean age was 5.36 ± 4.02 years in ALL patients and 5.93 ± 4.29 years in the healthy group. The boy/girl ratio was 17/16 and 16/14 in ALL and healthy groups, respectively. No remarkable differences were found between ALL and healthy groups concerning the age and gender distribution (P=0.52, using the *Student t*-test and P=0.98, using chi-square, respectively).

The effect of the treatment program on the IL-33 expression

In ALL patients, the pre-treatment serum IL-33 concentrations (33.89 ± 4.38 Pg/mL) were substantially greater than those in the healthy group (20.66 ± 2.20 Pg/mL, P<0.02, using the *Student t*-test). After completion of a treatment course, IL-33 concentrations were significantly reduced compared to pre-treatment levels (22.40 ± 2.60 Pg/mL versus 33.89 ± 4.38 Pg/mL; P<0.04, using *Student t*-test) (Table II and Figure 1A). Serum IL-33 levels did not differ markedly between the healthy group and the treated ALL patients (Figure 1A). The serum IL-33 concentrations in ALL patients and healthy persons according to their gender were also indicated in Table II. No significant differences were found between boys and girls either in ALL patients or in the healthy controls, concerning the serum IL-33 concentrations. In both boys and girls with ALL, there was a reduction in IL-33 concentrations after completing a course of treatment compared to pre-treatment levels (Table II and Figure 1B).

Likewise, the pre-treatment mRNA expression of IL-33 (1.79 ± 0.18) was considerably greater than that in the healthy controls (1.00 ± 0.10; P<0.001, using *Student t*-test). At the end of a treatment course, IL-33 mRNA expression (0.91 ± 0.15) was considerably diminished compared to the pre-treatment time (P<0.001, using *Student t*-test) (Table II and Figure 2A). In both ALL and control groups, no remarkable differences were detected between boys and girls concerning IL-33 mRNA expression (Table II). No remarkable difference was also found between the healthy group and the treated ALL patients considering mRNA expression of IL-33 (Figure 2A). In both boys and girls with ALL, there was a remarkable reduction in mRNA expression amounts of IL-33 at the end of treatment compared to pre-treatment levels (Table II and Figure 2B).

The impact of the treatment program on the ST2 expression

The mRNA expression levels of ST2 mRNA before treatment (1.42 ± 0.18) were remarkably greater than those in the healthy children (1.00 ± 0.09; P< 0.05, using *Student t*-test). In ALL patients, the mRNA expression of ST2 was reduced at the post-treatment time point (1.10 ± 0.11) compared to the pre-treatment time point, but the difference was not considerable (Table II and Figure 3A). In both ALL and controls, no remarkable difference was detected in ST2 mRNA expression between boys and girls (Table II). No considerable differences were found between the healthy controls and treated patients regarding the mRNA expression

[DOI: 10.18502/ijpho.v15i3.18920]

ST2. In both boys and girls with ALL, ST2 mRNA expression was reduced after treatment compared with before treatment, although this difference did not reach significance (Figure 3B).

Table I: Primer sets used to amplify IL-33 and ST2 mRNA.

Gene	Primer	Product size (bp)
IL-33	Forward: 5-GCAGGTGACGGTGTTGATGGTAAG-3	**100**
	Reverse: 5-GGAGCTCCACAGAGTGTTCCTTG-3	
ST2	Forward: 5-CAGGTACAGGGCGCACAAGTC-3	**150**
	Reverse: 5-CCTTGCTCATCCTTGACCGTGAAG-3	
β-Actin	Forward: 5-GCCGGGACCTGACTGACTAC-3	**100**
	Reverse: 5-TTCTCCTTAATGTCACGCACGAT-3	

Table II: Comparison of the serum IL-33 quantities, as well as mRNA expression of IL-33 and ST2 between ALL patients and healthy children according to gender.

Groups	Gender	Number	Serum IL-33 levels (Pg/ml)	IL-33 mRNA expression†	ST2 mRNA expression†	P value
ALL patients (Pre-treatment)	Boys	17	34.38 ± 7.09	1.75 ± 0.25	1.19 ± 0.17	●=0.11 ●●=0.025 ●●●=0.61 ■=0.09 ■■=0.001 ■■■=0.09
	Girls	16	33.35 ± 5.25	1.84 ± 0.27	1.66 ± 0.31	
	Total	33	33.89 ± 4.38	1.79 ± 0.18	1.42 ± 0.18	
	P value		*=0.90	**=0.80	***=0.20	
ALL patients (Post-treatment)	Boys	17	22.81 ± 3.61	1.10 ± 0.25	1.00 ± 0.13	
	Girls	16	21.95 ± 3.88	0.68 ± 0.16	1.23± 0.19	
	Total	33	22.40 ± 2.60	0.91 ± 0.15	1.10 ± 0.11	
	P value		*=0.84	**=0.18	***=0.31	
Healthy control group	Boys	16	20.50 ± 2.87	0.92 ± 0.12	1.07 ± 0.14	
	Girls	14	20.84 ± 3.60	1.09 ± 0.16	0.91 ± 0.12	
	Total	30	20.66 ± 2.20	1.00 ± 0.10	1.00 ± 0.10	
	P value		*=0.93	**=0.41	***=0.41	

† Expression amounts of mRNA were estimated as fold change and presented as mean ± SEM.

The *, ** and *** represent the difference in the serum IL-33 levels, expression of IL-33 mRNA and expression of ST2 mRNA, respectively between boys and girls in a specified group (using *Student-t* test). The ●, ●● and ●●● represent the inter-group comparisons regarding the differences of the serum IL-33 levels, expression of IL-33 mRNA and expression of ST2 mRNA, respectively in boys (using *ANOVA* test). The ■, ■■ and ■■■ represent the inter-group comparisons regarding the differences of the serum IL-33 levels, expression of IL-33 mRNA and expression of ST2 mRNA, respectively in girls (using *ANOVA* test).

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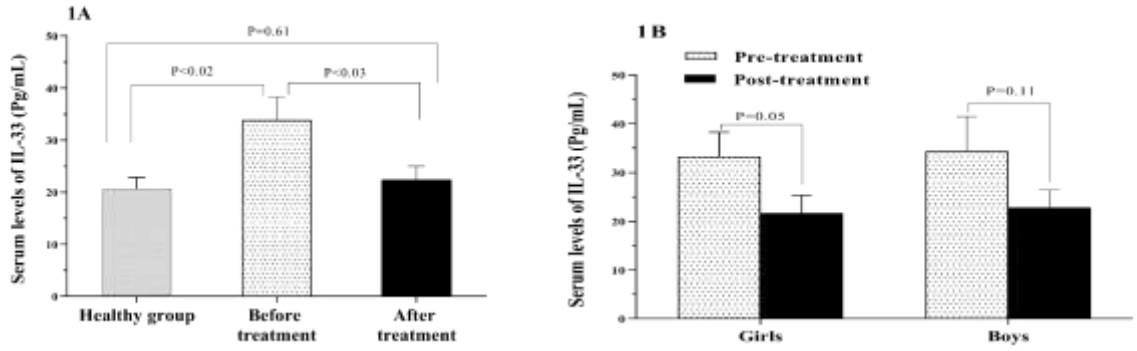

Figure 1. Comparison of the serum interleukin-33 levels between healthy individuals and ALL patients. 1A): Comparison of the IL-33 quantities measured before and following treatment. The serum IL-33 levels in untreated ALL patients were greater than control subjects (P<0.02, using the *Student t*-test). Treatment led to a remarkable reduction in IL-33 levels (P<0.03, using the *Student t*-test). No remarkable difference was detected between treated ALL patients and healthy individuals regarding the serum IL-33 amounts. 1B): Comparison of the IL-33 levels before and after treatment according to the gender of patients. Boys and girls exhibited lower IL-33 levels at post-treatment compared to pre-treatment (P=11 and P=0.05, respectively, using the *Student t*-test).

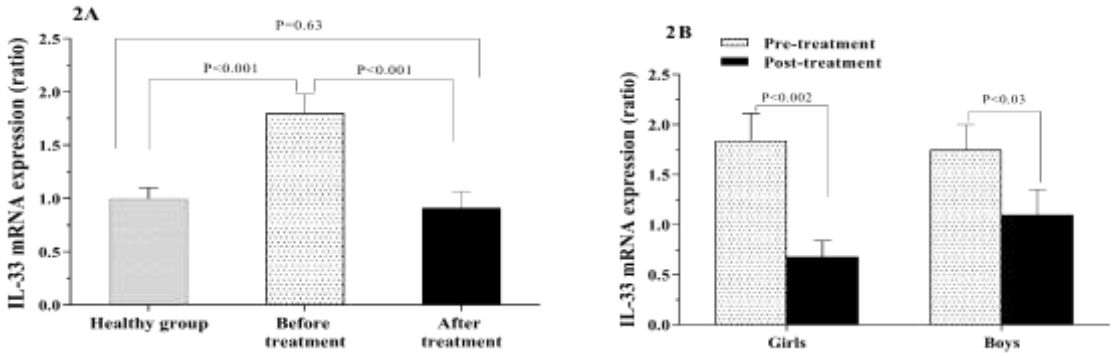

Figure 2. Comparison of the interleukin-33 mRNA expression between healthy children and ALL patients. 2A): Comparison of the IL-33 mRNA expression before and after treatment. The mRNA expression amounts of IL-33 in untreated ALL patients were higher than healthy subjects (P<0.001, using *Student t*-test). After treatment, the IL-33 mRNA expression levels were significantly reduced (P<0.001, using the *Student t*-test). No remarkable difference was detected between treated ALL patients and healthy controls regarding the mRNA expression of IL-33. 2B): Comparison of the IL-33 mRNA expression before and after treatment according to the gender of patients. Boys and girls exhibited lower IL-33 mRNA expression levels at post-treatment compared to pre-treatment (P<03 and P<0.002, respectively, using the *Student t*-test).

[DOI: 10.18502/ijpho.v15i3.18920]

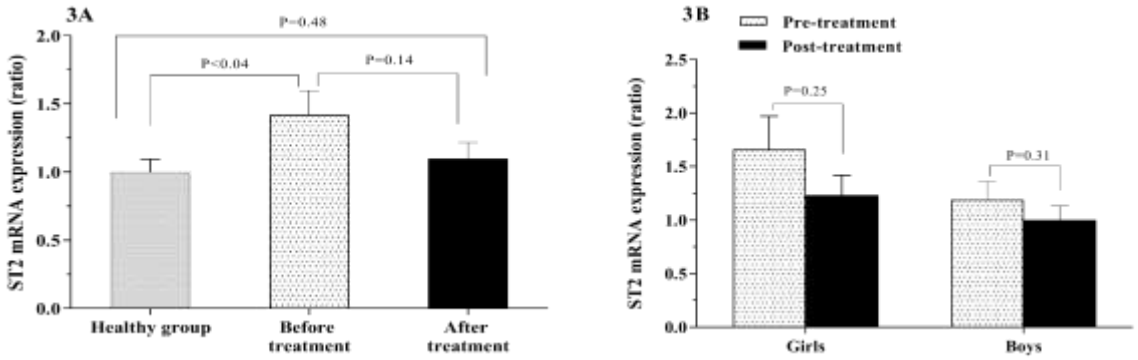

Figure 3. Comparison of the ST2 mRNA expression between healthy children and ALL patients. 3A): Comparison of the ST2 mRNA expression before and after treatment. The mRNA expression of ST2 in untreated ALL patients was higher than in healthy controls ($P<0.05$, using the *Student t*-test). After treatment, the ST2 mRNA expression was reduced, but the difference was not significant. No remarkable difference was observed between treated ALL patients and healthy groups regarding the mRNA expression of ST2. 3B): Comparison of the ST2 mRNA expression before and after treatment according to the gender of patients. In Boys and girls, no remarkable difference was observed between mRNA expression levels of ST2 at pre- and post-treatment times.

Discussion

The findings of this study revealed that newly diagnosed ALL patients had higher blood IL-33 concentrations, as well as higher IL-33 and ST2 mRNA expression. When compared to pre-treatment levels. Blood concentrations of IL-33 and mRNA expression of IL-33 were considerably reduced at the end of treatment. As a result, IL-33 can perform a crucial role in the genesis and progression of ALL.

The contribution of IL-33 to the hematological malignancies was also investigated in some studies. Musolino *et al.* indicated that patients with multiple myeloma had diminished IL-33 concentrations compared with healthy controls, and a reverse relation was found between IL-33 levels and multiple myeloma stages (28). Mager *et al.* indicated high proportions of the IL-33-expressing cells in tumor biopsies from patients with myeloproliferative neoplasms (MPN). The colony formation from $CD34^+$ MPN progenitor cells was also increased by IL-33 (29). Levescot *et al*. provided evidence that IL-33/ST2 signaling may contribute to the development of the CML progenitor cells (30).

However, the data from a study conducted by Stier *et al.* revealed that the expression of IL33 mRNA was decreased in B cell progenitors from patients with B cell chronic lymphocytic leukemia (B-CLL) compared with healthy controls. CLL patients also exhibited lower serum IL-33 quantities compared to healthy individuals (31). Thus, reduced expression of IL-33 in B-CLL from a threshold level can promote B-CLL development (31). Qin *et al.* showed that administering IL-33 to AML mice reduced the progression of malignancy by enhancing the anti-leukemia immune responses, such as promoting the number of leukemia-reactive $CD8^+$ cytotoxic T lymphocytes (CTLs) (32). These findings highlight the potential of IL-33 for immunotherapy in some hematologic malignancies. These aforementioned findings indicate that IL-33 can play pro- or anti-tumorigenesis in different types of hematologic malignancies. Polat *et al.* recently also observed elevated serum IL-33 and soluble ST2 concentrations in pediatric ALL patients compared to healthy individuals (33).

[DOI: 10.18502/ijpho.v15i3.18920]

Following a 5-day treatment program, IL-33 and soluble ST2 concentrations remained unchanged (33). Here, we observed that the administration of an induction chemotherapy course for 30 days to ALL patients leads to a remarkable reduction in the expression amounts of IL-33 mRNA and protein, suggesting that the duration of the treatment program may impact these levels. Moreover, IL-33 can operate as a biomarker for diagnosis and monitoring of the treatment efficacy in ALL patients. Consisting with the findings of the current study, greater amounts of IL-33 were also detected in the serum and tissue tumors of patients with gastric cancer, hepatocellular carcinoma, uterine leiomyoma, colorectal cancer, prostate cancer, lung cancer, breast cancer, and head and neck squamous cell carcinoma when compared to corresponding healthy tissues (14, 34, 35).

IL-33 can operate as a pro- and anti-tumor cytokine that is generated by malignant cells, fibroblasts, macrophages, and injured cells within the tumor microenvironment (36). IL-33 can promote tumor development by inducing Treg cells, M2 macrophages, cancer-associated fibroblasts (CAF), myeloid-derived suppressor cells (MDSCs), Th2 cells, angiogenesis, and mast cells, and by suppressing NK cells, NKT cells, and CTLs (36-40). However, Th1 cells, CTLs, NKT cells, and γδ T cells may all be stimulated by IL-33, which exerts anti-tumor properties (36). The expression of IL-33 and its receptor, ST2, in malignant tissues is powerfully related to the growth and progression of various kinds of cancer (41). IL-33/ST2-mediated signaling results in the production of pro-inflammatory cytokines and chemokines, which enhances cancer cell expansion, migration, and invasiveness as well as supports angiogenesis (41). The interaction between IL-33 and ST2 triggers the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), NF-κB and signal transducer and activator of transcription 5 (STAT5) pathways, which play a pivotal role in driving tumorigenic processes (26, 30, 42). Signaling pathways mediated by IL-33/ST2 increase cancer cell proliferation and viability while blocking apoptosis (26). IL-33 activates the p38 MAPK and AKT signaling pathways, which induce anti-apoptotic effects in childhood ALL cells (26). In the context of AML, IL-33-induced NF-κB pathway inhibits apoptosis and contributes to chemoresistance (42). Furthermore, STAT5 plays a critical role in the progression of ALL by promoting the proliferation of leukemic cells and inhibiting their apoptosis (26). IL-33 has been demonstrated to sustain proliferation and enhance drug resistance in leukemic precursors via a STAT5-dependent pathway (30). Targeting p38 MAPK, AKT, and STAT5 may inhibit IL-33-induced leukemic cell proliferation and increase their susceptibility to chemotherapy. When compared to wild-type mice, ST2-deficient mice with breast cancer display less metastasis, slower tumor growth, higher $CD8^+$ CTL and NK-mediated cytotoxicity, more intra-tumoral accumulation of $CD8^+$ CTLs and NK cells, and lower splenic M2 macrophage frequencies (40). M1 macrophage-derived IL-12 increases dendritic cell (DC) maturation and strengthens the Th1 cell responses, which activate CTLs, NK and NKT cells in ST2-defective animals (40). These observations represent that IL-33 can either directly promote cancer cell development or indirectly by repressing the anti-tumor immune responses.

Conclusion

Greater serum IL-33 concentrations were detected in ALL patients, suggesting that this cytokine may contribute to ALL progression. The clinical values of the IL-33 assessment in the ALL diagnosis,

[DOI: 10.18502/ijpho.v15i3.18920]

progression and prognosis need more consideration in future studies.

Data availability

Data are available upon request from authors.

Ethical Considerations

The study protocol was approved by the ethical committee of Kerman University of Medical Sciences and registered with an ethics code: IR.KMU.REC.1396.2228.

Acknowledgments

We would like to thank the pediatric Oncology unit nurses of Afzalipoor Hospital of Kerman for all their efforts. Artificial intelligence was not used to produce this article.

Authors' Contributions

AJ designed and conceptualized the study. MM performed the experiments. MM, AN, ZF, and NC aggregated the data. MM and AN analyzed the data. AJ wrote the manuscript. AJ scrutinized the scientific content. All authors read and approved the final manuscript.

Funding

This work was financially supported by a grant (NO: 96000784) from the Kerman University of Medical Sciences, Kerman, Iran.

Conflict of Interest

The authors declare no conflict of interest.

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[DOI: 10.18502/ijpho.v15i3.18920]