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Original Article

Interleukin-10 as the best biomarker to potential therapy targets in pediatric patients with acute lymphoblastic leukemia

María Teresa González-Garza[1,#,$], Erandi Pérez-Figueroa[1,2,#], Norma Sánchez-Zauco[1,3], Delia Elva Cruz-Vega[1], Carmen Madonado-Bernal[1,*]

[1]Laboratorio de Investigación en Inmunología y Proteómica, Hospital Infantil de México Federico Gómez, Dr. Márquez 162, Col. Doctores, 06720 Mexico City, Mexico; [2]Unidad Periférica para el Estudio de la Neuroinflamación en Patologías Neurológicas del Instituto de Investigaciones Biomédicas en el INNN, Mexico City, Mexico; [3]División de Auxiliares de Diagnóstico y Tratamiento UMAE, Hospital de Especialidades, Centro Médico Nacional-Siglo XXI, IMSS, Av. Cuauhtémoc 330, Col. Doctores, 06725 Mexico City, Mexico.

ABSTRACT

Chronic inflammation has been observed in patients with cancer, suggesting a possible alteration of the cytokine signaling pathway. The present study aims to identify potential cytokine markers in pediatric patients with acute lymphoblastic leukemia (ALL) classified as Pre-B, Pro-B, T and Bi phenotype. A total of 75 pediatric patients diagnosed with ALL were included in the present study, and divided into Pre-B, Pro-B, B, T and Bi phenotype groups. To determine the concentration of 13 cytokines and chemokines, 2 ml peripheral blood was collected by venipuncture. As a control, serum samples were obtained from 48 pediatric patients without a malignant, an infectious or immunological disease. Cytokine and chemokine levels in the serum from patients and control were quantified by multiplex analyte technology using the Millipore HCYTOMAG-60K kit. Analysis for the identification of potential biomarkers was performed using the PanelomiX software. The results revealed that interleukin-10 (IL-10) was the best biomarker in all immunophenotypes. Furthermore, other cytokines and chemokines, such as transforming growth factor β (TGF-β), interleukin-8 (IL-8), and tumor necrosis factor α (TNF-α), were detected in the Pre-B and Pro-B phenotypes. In the T phenotype, TNF-α and interferon-γ were detected as biomarkers in addition to IL-10. In the biphasic IL-10 phenotype, TNF-α and TGF-β were identified as biomarkers. The upregulation of cytokines suggests a phenomenon identified as 'cytokine release syndrome', which is a systemic inflammatory state described in infectious diseases, autoimmune diseases, and certain types of leukemia and lymphoma. The present study identified specific markers in each of the leukemic phenotypes studied, and provided a basis for the possibility of structuring chemotherapy more specifically to regulate cytokine expression, and to achieve the recovery of homeostasis.

KEYWORDS: acute lymphoblastic leukemia, biomarkers, IL-10, IL-8, TGF-β, TNF-α, IFN-γ.

INTRODUCTION

It has been reported that chronic inflammation can trigger events that induce malignant cell transformation and carcinogenesis [1-2]. Cytokines serve a crucial role and can control the development and

*Corresponding author: cmaldobe@yahoo.com
[#]Equal contribution
[$]In memory of our dear colleague Dr. María Teresa González-Garza.

multiplication of cancerous cells. Nevertheless, in cancer patients, the protective effect of cytokines against cancer, does not work. It has been proposed that during the pro-tumorigenic inflammatory state, feedback mechanisms increase cytokine synthesis, and most of these cytokines are involved in tumor-promoting mechanisms [3].

In order to understand this phenomenon, several investigations have been performed, and these examined the role of cytokines during the establishment, multiplication and dissemination of cancer cells. Cytokines serve a central role in inflammation processes. Based on the abnormal serum cytokine levels observed in patients with cancer, it has been suggested that signaling pathways are altered. Patients with different malignancies exhibit altered expression levels of pro-inflammatory and anti-inflammatory cytokines [4-7]. The possibility of regulating cytokine levels in patients with cancer has allowed the development of novel therapies for an optimal treatment approach, independent of the immunophenotype or molecular genetics of the patients. An important point of focus has been the application of antibodies against a number of cytokines and chemokines, such as interleukin-10 (IL-10), transforming growth factor β (TGF-β) and tumor necrosis factor α (TNF-α), or against their signaling pathways [8, 9].

IL-10 is an anti-inflammatory cytokine. It inhibits the production of proinflammatory cytokines such as IL-1β and TNF-α and antigen presentation to T cells *via* other cytokines [10]. Furthermore, its upregulation is associated with tumorigenesis, autoimmunity and transplantation resistance [11]. Its possible role as a central pivot of cancer cell establishment has made it the focus of several *in vitro*, *in vivo* and clinical studies. Another target cytokine is TNF-α, a potent pleiotropic pro-inflammatory cytokine with multiple functions. It is secreted from monocytes and serves an essential role in autoimmune diseases [12]. Notably, increasing evidence has demonstrated that TNF-α can promote the survival, proliferation and migration of cancer cells. Infliximab, a chimeric monoclonal antibody against TNF-α, has been applied to treat severe rheumatoid arthritis, central nervous system sarcoidosis, psoriasis and Crohn's disease, in which certain clinical benefits were provided [13]. *In vitro* and *in vivo* evaluation of anti-TNF-α (infliximab) chemotherapy in human colon cancer, pancreatic ductal adenocarcinoma tissue samples and colon cancer cell lines has suggested a possible benefit to patients with cancer [14, 15]. However, clinical trials in patients with metastatic non-small cell lung cancer and pancreatic cancer did not reveal any benefits [16, 17].

At present, therapeutic approaches are directed against one type of inflammatory cytokine, such as IL-10 or TNF-α, and complemented with one or two cytotoxic drugs. However, the possibility of external balancing of two or more cytokines could allow the recovery of the immune surveillance system. Therefore, it is important to determine which ones are mainly altered, either by upregulation or depletion. In our previous study, the inflammatory state in children with acute lymphoblastic leukemia (ALL) was strong and deregulated with a Th1-polarization profile and was not associated with infection [18]. The present study aims to identify cytokine markers in the Pro-B, Pre-B, T and Bi phenotypes in pediatric patients with ALL, which may be used for targeted therapy.

PATIENTS, MATERIALS AND METHODS

Patients

A total of 75 pediatric patients diagnosed with ALL at the Hospital Infantil de Mexico Federico Gomez, Mexico, City, were included in the present study. We confirmed that patients with ALL included in this study had no apparent clinical infection at diagnosis, the point at which blood samples used in this study were taken. We conducted a detailed review of the clinical records to confirm that the specimens of patients with ALL were negative for all microbiological tests of blood, urine, and spinal fluid (LCR) by culture and/or polymerase chain reaction. We excluded children who had infection at the time of diagnosis, or who had anti-inflammatory, antimicrobial, or antineoplastic treatment. We also excluded children with immunodeficiencies or recent transfusion of blood components. The study was approved by the Research and Ethics Committees of the Hospital Infantil de México Federico Gómez, Mexico City. Informed and signed consent of the patients' guardians was obtained as well as the assent of children over 9 years old. The samples were

obtained between March 18, 2011 and November 10, 2013. The age of the patients was between 0.25 and 17.83 years (Mean 7.58 ± 4.63), and there were 35 male and 40 female patients. The patients were classified according to their phenotype as Pre-B, Pro-B, B, T and Bi phenotype. Cytokine quantification of patients with ALL was performed before their first chemotherapy and radiotherapy treatment. A total of 2 ml peripheral blood was obtained by venipuncture, and the sera were obtained by centrifugation at 1,000 x g for 10 min at 4 ˚C. Serum samples were stored at -80 ˚C until analysis. As a control, 48 samples from pediatric patients aged between 0.25 and 17 years (mean 9.14 ± 3.94) were obtained, including 22 male and 24 female patients, who were attended in the Department of Orthopedics or Ophthalmology of the Hospital Infantil de México Federico Gómez, without malignant, infectious or immunological diseases.

Determination of the concentration of serum cytokines and chemokines

Cytokines and chemokines, including interleukin-1 (IL-1β), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), interleukin-10 (IL-10), interferon-γ (IFN-γ), interleukin-12 (IL-12), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-13 (IL-13), transforming growth factor-β (TGF-β) and interleukin-17 (IL-17), were quantified in the sera of patients and controls by multiplex analyte profiling technology using the Millipore HCYTOMAG-60K kit (Luminex®; magnetic beads; EMD Millipore), and were read on a MAGPIX apparatus (Milliplex®; EMD Millipore). All reagents were prepared according to the manufacturer's protocol. All samples were analyzed in duplicate, and the mean concentration of each cytokine or chemokine was determined using a parameter logistic fitted curve generated from the standards included in the kit.

Statistical analysis

All statistical analyses were performed, and graphs were generated, using the R programming language Version 4.0.3 (http://www.r-project.org/). For the biomarker panel analysis, PanelomiX Version 1.1, a threshold-based algorithm, was applied to determine the cytokine concentration for each immunophenotype group [19].

RESULTS

Frequency of immunophenotypes

The most frequent immunophenotype in the study group was Pre-B (33.78%), followed by Pro-B (21.62%) and T (29.73%) immunophenotypes. The Bi phenotype was less frequent (16.22%). Only 3 patients in the study group were diagnosed as B phenotype. For statistical analyses, this group was excluded (Fig. 1). To identify markers that

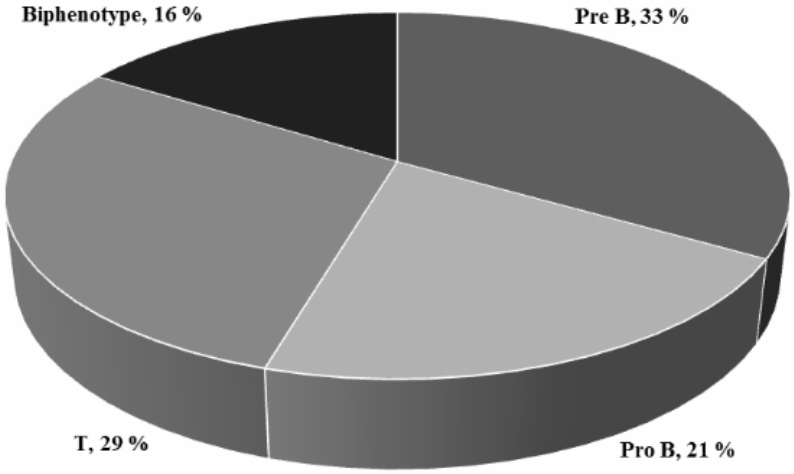
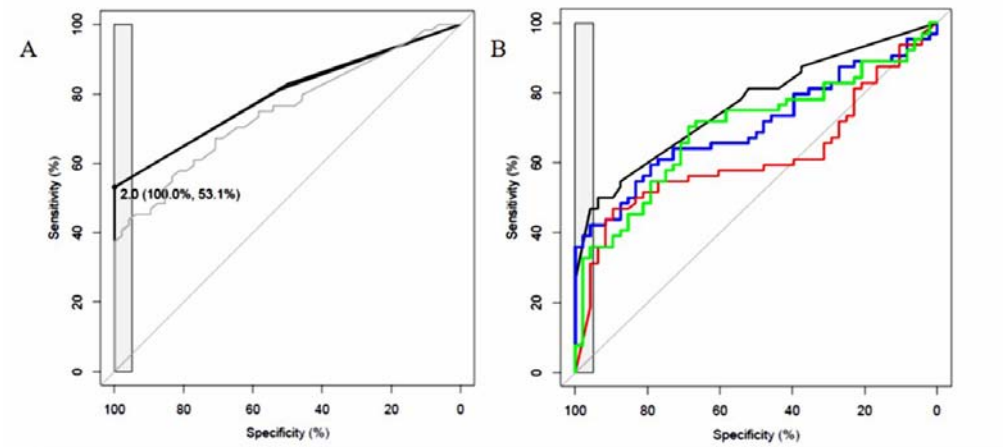


Fig. 1. Percentages of phenotypes among pediatric patients diagnosed with acute lymphoblastic leukemia. The Pre-B type was the most frequent and the Bi immunophenotype was the least frequent.



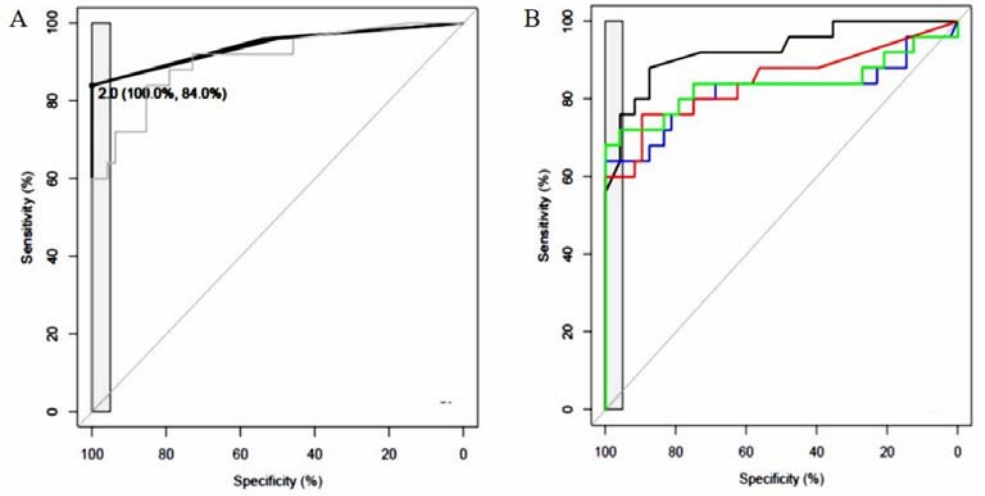
C

Marker	%pAUC (95% CI)	Threshold	% SP (95% CI)	%SE (95% CI)	P-value
IL-10	2.0 (1.4-2.7)	52.9	98.8 (89.6-100.0)	43.8 (31.2-56.7)	--
Panel	2.7 (2.1-3.3)	1.5	100.0 (100.0-100.0)	53.1 (40.6-65.6)	0.00536

D

	IL-10	TGF-β	IL-8
Panel 1	>74.283	<1239	>22.417
Panel 2	>65.791	<1239	>27.665

Fig. 2



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Marker	%pAUC (95% CI)	Threshold	% SP (95% CI)	%SE (95% CI)	P-value
IL-10	3.0 (2.2-4.2)	78.425	100.0 (100.0-100.0)	60.0 (40.0-80.0)	--
Panel	4.2 (3.5-4.8)	1.5	100.0 (100.0-100.0)	84.0 (68.0-96.0)	0.0468

D

	IL-10	TNFα	TGFβ	IL-8
Panel 1	>17.73	>60.315	<1847	----
Panel 2	>78.425	-----	<1239	>27.665
Panel 3	>78.425	-------	<1239	>22.42

Fig. 3

could distinguish among the different immunophenotypes, data were analyzed using the PanelomiX program.

Analysis of markers for the Pre-B immunophenotype

The cytokine analysis in this group identified two different groups of data. IL-10 was the best biomarker determined by receiver operating characteristic (ROC) analysis with a high specificity (100%) and medium sensitivity (53.1%; Fig. 2A). Comparisons with other standard methods, such as logistic regression and recursive partitioning, are shown in Fig. 2B. ROC analysis of the best biomarker and the Pre-B immunophenotype panel (Fig. 2C) demonstrated that IL-10 (>65.79 pg/mL) was the best biomarker. Additionally, TGF-β (<1,239 pg/mL) was identified as a biomarker, and IL-8 (>22.42 pg/mL) was also revealed as a biomarker (Fig. 2D). The other cytokines studied did not appear to be biomarkers for this ALL immunophenotype.

Analysis of markers for the Pro-B immunophenotype

The cytokine analysis in this group identified three different groups of data. IL-10 was the best biomarker according to ROC analysis, with a high specificity (100%) and sensitivity (84%; Fig. 3A). The comparison with other standard methods, such as logistic regression and recursive partitioning, is shown in Fig. 3B, revealing the sensitivity and specificity. ROC analysis of the Pro-B immunophenotype panel revealed that IL-10 was the best biomarker (Fig. 3C) as determined by the PanelomiX software. The analysis determining cytokine marker values demonstrated that an IL-10 concentration >17.73 pg/mL was associated with higher values of TNF-α (>60.315 pg/mL) and TGF-β (<1,847 pg/mL). However, the IL-10 value was >78.425 pg/mL and TGF-β was <1,239 pg/mL. The result was considered positive when the levels of any of the two markers were above or below the given concentration (Fig. 3D). In most of the cases, there were no biomarker differences between the Pro-B and Pre-B immunophenotypes. The other cytokines studied did not appear to be biomarkers for this ALL immunophenotype.

Analysis of markers for the T immunophenotype

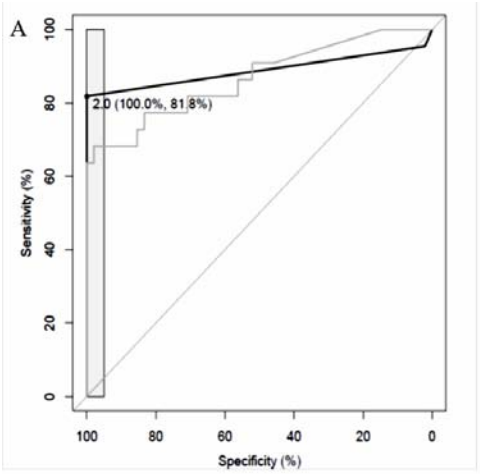
The T immunophenotype ROC curves are shown in Fig. 4A, revealing a high specificity (100%) and medium sensitivity (81.8%) for IL-10. The comparison with other standard methods, such as logistic regression and recursive partitioning, is shown in Fig. 4B. ROC analysis of the best biomarker using PanelomiX revealed the highest concentrations for IL-10 (>80.00 pg/mL) and TNF-α (>43.96 pg/mL; Fig. 4C). Additionally, a different biomarker from those for the Pro-B and Pre-B immunophenotypes was identified in this group: IFN-γ (<34.13 pg/mL). IL-8 was not considered to be a biomarker (Fig. 4D). And the other cytokines studied, did not appear to be biomarkers for this ALL immunophenotype.

Analysis of markers for the Biphenotype

The ROC curve analysis for markers in the Bi phenotype is shown in Fig. 5A. The analysis

Legend to Fig. 2. ROC curves for the Pre-B immunophenotype cytokine panel 1. (A) Sensitivity and specificity for IL-10 analysis. (B) ROC curves showing comparison with other combination methods. Black, PanelomiX; blue, logistic regression; green, support vector machine; red, recursive partitioning. (C) Table from ROC analysis of the best biomarker for the Pro-B immunophenotype as determined by PanelomiX software. (D) Table of cytokine concentrations as markers as determined by PanelomiX software. The result was considered positive when any two markers coincided. ROC, receiver operating characteristic.

Legend to Fig. 3. ROC curves for the Pro-B immunophenotype cytokine panel. (A) Sensitivity and specificity for IL-10 analysis. Black, cytokine panel; grey, IL-10. (B) ROC curves showing comparison with other combination methods. Black, PanelomiX; blue, logistic regression; green, support vector machine; red, recursive partitioning. (C) Table from ROC analysis of the best biomarker for the Pro-B immunophenotype as determined by PanelomiX software. (D) Table of cytokine concentrations as markers as determined by PanelomiX software. The result was considered positive when any two markers coincided. ROC, receiver operating characteristic.



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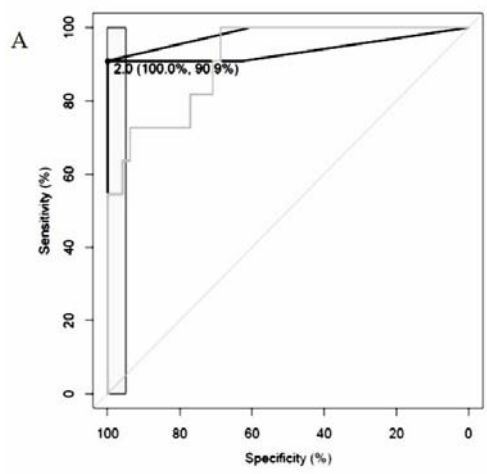
Marker	%pAUC (95% CI)	Threshold	% SP (95% CI)	%SE (95% CI)	P-value
IL-10	3.3 (2.3-4.3)	66.85	97.9 (93.8-100.0)	68.2 (50.0-86.4)	--
Panel	4.1 (3.2-4.8)	1.5	100.0 (100.0-100.0)	81.8 (63.3-95.5)	0.23007

D

Panel 1	IL-10	TNF-α	IFNγ
	>80.00	>43.96	<34.13

Fig. 4. ROC curves for the T immunophenotype cytokine panel 1. (A) Sensitivity and specificity for IL-10 analysis. (B) ROC curves showing comparison with other combination methods. Black, PanelomiX; blue, logistic regression; green, support vector machine; red, recursive partitioning. (C) ROC analysis of the best biomarker for the T immunophenotype as determined by PanelomiX software. (D) Cytokine concentrations as markers as determined by PanelomiX software. The result was considered positive when any two markers coincided. ROC, receiver operating characteristic.



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Marker	%pAUC (95% CI)	Threshold	% SP (95% CI)	%SE (95% CI)	P-value
IL-10	2.8 (1.4-4.4)	52.305	95.8 (89.6-100.0)	63.6 (36.4-90.9)	--
Panel	4.6 (37-5.0)	1.5	100.0 (100.0-100.0)	90.9 (72.7-100)	0.04573

D

	IL-10	TNF-α	TGF-β
Panel 1	>9.59	>55.75	<17.25

Fig. 5

revealed a high specificity (100%) and sensitivity (90.9%) for IL-10. The comparison with other standard methods, such as logistic regression and recursive partitioning, is shown in Fig. 5B. The ROC analysis of the best biomarker and the panel for the Bi phenotype using PanelomiX software revealed that IL-10 was the best marker (Fig. 5C). The biomarker panel results are shown in Fig. 5D. Among the biomarkers, as for the other immunophenotypes, IL-10 was the best biomarker according to ROC analysis. However, its concentration was lower compared with that in the other groups. The other cytokines studied did not appear to be biomarkers for this ALL immunophenotype.

Analysis of markers for the Pre-B and Pro-B immunophenotypes

According to PanelomiX analysis, the Pro-B and Pre-B immunophenotypes presented similar markers, except in the Pro-B panel 1. In addition, IL-10 was a marker at lower concentrations (17.73 pg/mL), and the presence of TNF-α at concentrations >60,315 pg/mL was identified as a marker. In this panel, IL-8 was not detected as a marker. In the T immunophenotype, IFN-γ was revealed as a marker in addition to IL-10 and TNF-α. In patients diagnosed as Bi phenotype, the markers were similar to those of patients diagnosed as Pre-B and Pro-B. However, they appeared from lower concentrations. IL-10, in certain cases (panel 1), presented similar values as the control. The main difference was the presence of IFN-γ and TNF-α as markers in the T immunophenotype group (Table 1).

No association was observed between age, sex or body weight and IL-10 cytokine concentration.

DISCUSSION

Analysis identifying potential biomarkers in ALL with different immunophenotypes was performed using PanelomiX software. Therefore, the serum concentration of 13 cytokines was investigated. The results demonstrated that IL-10 was the best biomarker in all immunophenotypes. Other cytokines and chemokines, including TGF-β, IL-8, TNF-α and IFN-γ, were identified as potential biomarkers, depending on the immunophenotype. The other cytokines studied (IL-1β, IL-6, MCP-1, IL-12, IL-2, L-4, IL-13 and IL-17) did not appear to be biomarkers.

IL-10 is synthesized by several cells, such as macrophages, monocytes, dendritic cells, mast cells, neutrophils, eosinophils, natural killer cells and T helper cells. In a feedback mechanism, it induces the inhibition of the expression of inflammatory cytokines by those cells [20]. TGF-β and IL-8 complete this regulatory mechanism in the B immunophenotype, as a group of biomarkers. In the T immunophenotype, IL-10, TNF-α and IFN-γ were identified as biomarkers.

It has also been suggested that detection of IL-10 could be performed in tumor cells [21]. *In vitro* studies have suggested that melanoma cells themselves are the primary origin of IL-10 in organisms [22, 23]. Additionally, IL-10 and IL10R are found in cells surrounding lung tumor cells and non-small-cell lung cancer in surgical specimens [24].

In patients with Hodgkin's disease, the serum concentrations of IL-10 are elevated and associated with poor survival, which suggests that IL-10 may serve as an independent prognostic factor [25]. Pediatric patients with Hodgkin's disease express high levels of IL10 mRNA in the lymph nodes, and these are associated with an unfavorable prognosis [26]. In Non-Hodgkin's disease, high levels of IL-10 are associated with a poor prognosis [27].

Since high levels of Janus kinase (JAK)/STAT signaling pathway-related serum cytokines (IL-6, IL-10, epidermal growth factor and IL-2) have been observed in patients with diffuse large B-cell

Legend to Fig. 5. ROC curves for the Biphenotype cytokine panel. (A) Sensitivity and specificity for IL-10 analysis. (B) ROC curves showing comparison with other combination methods. Black, PanelomiX; blue, logistic regression; green, support vector machine; red, recursive partitioning. (C) ROC analysis of the best biomarker for the Bi phenotype as determined by PanelomiX software. (D) Table of cytokine concentrations as markers as determined by PanelomiX software. The result was considered positive when any two markers coincided. ROC, receiver operating characteristic.

Table 1. Cytokine markers determined by PanelomiX software according to the immunophenotype.

	IL-10 pg/ml	**TNFα** pg/ml	**TGFβ** pg/ml	**IL-8** pg/ml	**IFNγ** pg/ml
Pro- B1	>17.73	>60.31	<1 847	----	-------
Pro- B 2	>78.42	-----	<1 239	>27.66	-------
Pro- B 3	>78.42	-------	<1 239	>22.42	------
Pre-B1	>74.28	-----	<1 239	>22.42	------
Pre-B2	>65.79	-----	<1 239	>27.66	-----
T	>80.00	>43.95	-----	----	<34.12
Biphenotype1	>9.59	>55.75	<17.25	------	-----
Biphenotype 2	>47.78	>29.48	<17.25	------	------
Control	13.8 ± 18.1	24.7 ± 31.7	ND	8.02 ± 15.2	6.44 ± 7.20

lymphoma, serum IL-10 could be a candidate for JAK2-targeted therapy [28].

To improve the understanding of the IL-10 mechanisms, a gene silencing technique against IL-10 expression has been applied *in vitro* in a breast cancer cell line and B-cell non-Hodgkin's lymphoma.

The results demonstrated that the apoptosis of cancer cells is associated with downregulation of PI3K/AKT and Bcl2 gene expression, and an increase in BCL2 binding component 3, BAX, caspase 3 and cleaved-caspase 3 expression [29, 30].

In the present study, using the Palelomix program, it was revealed that IL-10 was the best marker for ALL. Additionally, high concentrations of TGF-β and IL-8 were detected in the B immunophenotype. TGF-β is a pleiotropic cytokine that serves an important role in cancer progression [8, 31]. In these immunophenotype groups, IL-8 expression was identified to be elevated and to be a marker. This is a chemokine whose primary function is the attraction of immune cells, and it is associated with poor response to chemotherapy in patients with cancer [32-35].

In the T immunophenotype group, in addition to IL-10, TNF-α and IFN-γ concentrations were increased in the serum. TNF-α is a potent pleiotropic cytokine with multiple cellular functions. It acts in autocrine, paracrine and systemic ways. It has been implicated in the genesis of inflammation, autoimmunity, and cancer *via* the expression of several genes [36]. Clinical trials have investigated its potential benefits. It improves/stabilizes weight loss in elderly and poor performance status patients with metastatic non-small cell lung cancer. However, it is associated with increased fatigue and inferior global quality of life [17].

Other studies investigating cytokine interrelations have reported that IL-1β and TNF-α strongly enhance IL-6 release from renal cell carcinoma cells, but only marginally affect IL-10 production in colon carcinoma cells. IL-10 secretion of colon carcinoma cells is moderately stimulated by IFN-γ and IL-4 [37].

Macrophages are initially involved in the homeostatic processes of tissue resorption and the acquisition of nutrients. It is known that these cells are involved in multiple immunological functions, as well as in maintaining tissue integrity. They are sensitive to a number of cytokines, such as IFN-γ and IL-4, which induce its activation and respond by TNF-α and IL-6 secretion. IL-6, in combination with IFN-γ, enhances the production of the pro-inflammatory cytokines IL-1β and TNF-α. However, in the autocrine signaling pathway, IL-10, an anti-inflammatory cytokine, is involved in cytokine regulation [38].

Although there was a different cytokine/chemokine profile between immunophenotypes B and T, the present study demonstrated that IL-10 was the best biomarker in both groups and increased the expression of other cytokines and chemokines.

Alterations in cytokine expression have been extensively described in infectious diseases,

autoimmune diseases, and certain types of leukemia and lymphoma. It is described as a cytokine storm. An excessive or uncontrolled release of pro-inflammatory cytokines is well known and has been used in therapeutic strategies. IFNs and TNF inhibitors have been applied to prevent the storm and for treatment when it has already started. There are other therapeutic targets against the cytokine storm such as the chemokine network and the cholinergic anti-inflammatory signaling pathway. Nevertheless, at present, there is no consensus on the treatment of cytokine storms in infectious diseases [39-41].

CONCLUSION

In oncological diseases, the immunotherapy approach could induce a phenomenon identified as ‘cytokine release syndrome’. This is a systemic inflammatory state observed after strategic immunotherapies, mainly due to the use of bispecific antibodies, chimeric antigen receptor antibodies, high mobility group box 1 (HMGB1) antibodies, and cyclooxygenase-2 inhibitors. In addition, it has been implemented against several hematologic malignancies, including in pediatric patients.

The present study identified the specific markers in each of the leukemia phenotypes studied and suggested the possibility of structuring specific chemotherapy to regulate cytokine expression such as IL-10 and achieve homeostasis recovery.

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AUTHOR CONTRIBUTION STATEMENT

MTGG - conception, statistical analysis and interpretation, drafting the manuscript, gave final approval of the version to be published. EPF - acquisition of samples and data, performed quantification of cytokine concentration. NSZ - acquisition of samples data, performed quantification of cytokine concentration. DECV - revised it critically for important intellectual content, gave final approval of the version to be published. CMB - conception, revised it critically for important intellectual content, gave final approval of the version to be published.

AVAILABILITY OF DATA AND MATERIALS

The datasets used during the present study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethic Committee from the Hospital Infantil de México Federico Gómez. Informed written consent was obtained from all legal guardians of patients prior to enrollment in the study, and assent was obtained from all children older than 9 years of age.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no competing interests regarding the publication of this article.

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