

Influence of Chemotherapy on Allergen-Specific IgE

Sarah Whiteside^a Marketa Markova^b Alex Chin^{a, c} Cynthia Lam^a
Poonam Dharmani-Khan^{a, c} Monica Modi^a Faisal Khan^{a, c} Jan Storek^a

^aDepartment of Medicine, University of Calgary, Calgary, AB, Canada; ^bInstitute of Hematology and Blood Transfusion, Prague, Czech Republic; ^cCalgary Laboratory Services, Calgary, AB, Canada

Keywords

Atopy · B lymphocytes · Chemotherapy · IgE · Plasma cells

Abstract

Background: Atopy is defined as excess allergen-specific IgE (A-IgE). IgE is produced by plasma cells that differentiate from allergen-specific B cells. B cells are known to be killed by chemotherapy; however, it is not known whether A-IgE-secreting plasma cells are killed or inhibited by chemotherapy. If yes, serum A-IgE levels would be expected to decrease after chemotherapy. **Objectives:** We aimed to determine whether A-IgE levels in atopic individuals (serum A-IgE ≥ 0.35 kU_A/L) decrease into the nonatopic range (< 0.35 kU_A/L) after chemotherapy. **Methods:** In 105 patients undergoing chemotherapy for acute leukemia, we measured serum A-IgE before and after chemotherapy. In a subset of these patients, we also measured B cell counts before and after chemotherapy. **Results:** Of the 105 patients, 36 were atopic. In these patients, median A-IgE level before chemotherapy was 1.6 kU_A/L whereas the median level after chemotherapy was 0.6 kU_A/L ($p < 0.001$). In 12/36 (33%) patients, A-IgE levels decreased into the nonatopic range. In nonatopic patients ($n =$

69), the median A-IgE level also dropped: from 0.04 kU_A/L before to 0.03 kU_A/L after chemotherapy ($p = 0.001$). Among the total patients ($n = 105$), the median pre:post-chemotherapy A-IgE ratio was 1.8 (2.6 in atopic and 1.5 in nonatopic patients). In contrast, the median ratio of pre:post-chemotherapy B cell counts was 87.6. **Conclusions:** A-IgE levels decrease after chemotherapy but markedly less than B cell counts. Thus, at least some A-IgE plasma cells appear to survive chemotherapy.

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Introduction

Excess of allergen-specific IgE (A-IgE), here defined as serum level ≥ 0.35 kU_A/L (kilounits of antibody per liter), is referred to as atopy. Atopy may manifest as allergic disease (e.g., asthma, rhinitis, or eczema). A-IgE is produced by plasma cells that differentiate from allergen-specific B cells. It is not known whether the A-IgE-producing plas-

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Table 1. Patient characteristics

Atopic/nonatopic patients	36/69
Median age (range), years	48 (19–65)
Sex, males/females	60/45
Diagnosis	
Acute myeloid leukemia	79
Acute lymphoid leukemia	18
Acute biphenotypic leukemia	4
Chronic myeloid leukemia	
Blast phase	1
Advanced	1
Myelodysplastic syndrome (advanced)	1
Burkitt's lymphoma	1
Chemotherapy ¹	
1 cycle	7
2 cycles	30
3 cycles	40
4 cycles	23
5 cycles	2
6 cycles	2
7 cycles	1
Corticosteroid included ² yes/no	22/83

¹ Number of chemotherapy cycles between pre- and post-blood sampling. For myeloid malignancies, therapy typically consisted of a cycle of induction chemotherapy with idarubicin (12 mg/m² daily on days 1–3) plus cytarabine (200 mg/m² daily on days 1–7), followed by up to 4 cycles of consolidation chemotherapy with high-dose cytarabine (3 g/m² every 12 h on days 1, 3 and 5 of each cycle). For lymphoid and biphenotypic malignancies, a variety of regimens were used, frequently including an anthracycline, vincristine, asparaginase, methotrexate, and a corticosteroid.

² Discounting corticosteroids given purely as anti-emetics.

ma cells are short-lived and thus in atopic individuals frequently replenished from A-IgE B cells (repeatedly exposed to and thus stimulated by allergens) versus whether the A-IgE plasma cells are long-lived, keeping serum A-IgE levels in the atopic range (≥ 0.35 kU_A/L) even without frequent replenishment from A-IgE B cells. Chemotherapy is expected to kill B cell precursors and B cells [1, 2]. However, serum IgG levels are not substantially decreased after chemotherapy [3, 4] because IgG plasma cells are long-lived and relatively chemoresistant [5–8]. It is unknown whether this applies also to IgE plasma cells in humans.

Here, we set out to determine whether A-IgE levels decline into the nonatopic range (<0.35 kU_A/L) in atopic patients (A-IgE ≥ 0.35 kU_A/L) undergoing chemotherapy for acute leukemia. Our hypothesis was that A-IgE levels do not decline, based on a murine model in which A-IgE did not decline after cyclophosphamide treatment [9] as

well as studies in patients with a history of filarial infection in whom filarial-specific IgE was shown to persist for ≥ 5 years after successful treatment without reexposure to filaria [10].

A secondary goal of this study was to determine whether A-IgE levels rise after chemotherapy to the atopic range in patients with A-IgE levels in the nonatopic range (non-atopic patients). Our hypothesis was that the levels do not rise, as these patients are presumably nonatopic irrespective of chemotherapy. On the other hand, chemotherapy may be associated with immune dysregulation [11–13]. Consistent with that, elevated total IgE levels were found in some patients after chemotherapy with autologous or syngeneic stem cell transplantation [14].

Altogether it is not known whether A-IgE levels rise or decline after chemotherapy. Here, we aimed to evaluate this issue in patients receiving chemotherapy for acute leukemia.

Materials and Methods

Patients

Patients about to undergo chemotherapy for acute leukemia were asked whether their serum A-IgE could be measured before induction chemotherapy and after approximately of 2–3 cycles of chemotherapy. A total of 105 patients were accrued. Their demographic and clinical characteristics are displayed in Table 1. As obtaining consent from some patients before starting the induction chemotherapy was logistically challenging, we allowed the “pre-chemotherapy” specimen to be obtained up to 7 days after starting induction chemotherapy.

IgE Level Determination

A-IgE serum levels were determined using the ImmunoCAP Phadiatop test (Thermo Fisher Scientific Inc., Uppsala, Sweden). This test measures A-IgE against multiple common aeroallergens, i.e., specifically allergens extracted from *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat, dog, and horse dander, timothy grass, mugwort, pellitory-of-the-wall (upright pellitory), birch and olive tree pollen, and *Cladosporium herbarum* mold. The solid phase of ImmunoCAP is covalently coupled to standardized allergen source material, recombinant allergen components, or relevant markers to the respective allergen of interest. This solid phase also consists of an optimal amount of cellulose to ensure binding of all relevant IgE antibodies in the patient's sample. IgE in serum samples binds to the allergens on the solid phase. After washing out nonspecific IgE, mouse anti-human IgE (secondary antibody) bound to an enzyme is added to form a complex, and then an enzyme substrate is added, resulting in a fluorescent signal. A-IgE concentration is determined using a standard curve, created by dilution of a known concentration of purified A-IgE over a range of concentrations.

Total IgE serum levels were determined by the Roche Cobas Elecsys IgE II assay. This method is based on the sandwich principle where IgE in the sample, a biotinylated murine monoclonal

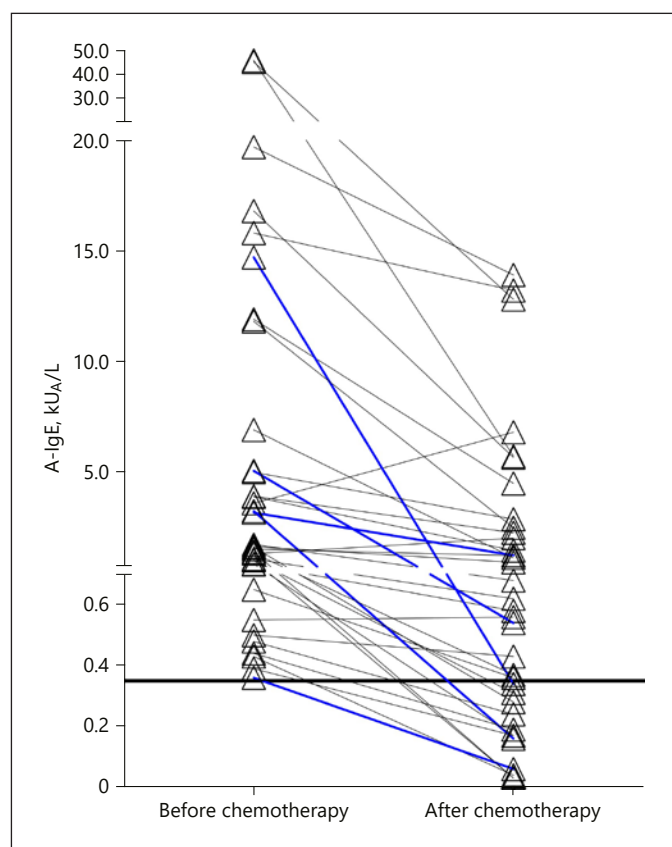


Fig. 1. Allergen-specific IgE (A-IgE) levels before and after chemotherapy in atopic patients ($n = 36$). The horizontal line indicates the cutoff ($0.35 \text{ kU}_A/\text{L}$) between the atopic and nonatopic A-IgE range. As the lower limit of detection is approximately $0.1 \text{ kU}_A/\text{L}$, all values $<0.1 \text{ kU}_A/\text{L}$ are arbitrarily assigned a value of $0.05 \text{ kU}_A/\text{L}$. Patients who received ≥ 1 cycle of chemotherapy containing a corticosteroid are indicated in blue.

IgE-specific antibody, and a murine monoclonal IgE-specific antibody labeled with a ruthenium complex form a sandwich complex. After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the electrode surface. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

B Cell Enumeration

This was done only in a subset of patients for whom cryopreserved blood mononuclear cell (MNC) levels were available from both the pre- and the post-chemotherapy time points. B-cell acute lymphoid leukemia (ALL) patients were excluded as in pre-chemotherapy specimens B cells could not be reliably distinguished from B lymphoblasts. The number of patients analyzed was 12. Heparinized blood was drawn at the same time points as the anti-

coagulated blood for serum (to measure A-IgE). For the pre-chemotherapy time point, this was a median of 0 days before starting chemotherapy (range, 16 days before to 7 days after starting chemotherapy). For the post-chemotherapy time point, this was a median of 48 days after starting the last chemotherapy cycle (range, 30–72 days). MNCs were separated using Lympholyte (Cedarlane, Burlington, ON, Canada). MNCs were stained with CD19 and CD20 monoclonal antibodies, both conjugated with phycoerythrin (clone J3-119 for CD19-PE and clone 2H7 for CD20-PE from Beckman Coulter, Miami, FL, USA, and Thermo Fisher Scientific, Canada, respectively). Percent B cells (CD19+ and/or CD20+ cells) among MNCs were determined using flow cytometry. Absolute B cell count was calculated as the absolute count of MNCs (lymphocytes + monocytes + blasts) determined by a clinical hematology laboratory $\times$ percent B cells/100.

Statistics

Significant differences in A-IgE levels, total IgE levels, or B cell counts between before versus after chemotherapy were tested using the Wilcoxon paired test. Significant differences in pre:post-chemotherapy A-IgE ratios between patient subgroups (e.g., patients with versus without corticosteroid as part of chemotherapy) were tested using the Mann-Whitney rank sum test.

Results

Effect of Chemotherapy on A-IgE in Atopic Patients

Of the 105 patients, 36 were atopic. In virtually all atopic patients, A-IgE levels declined after chemotherapy. The median pre-chemotherapy A-IgE level was $1.595 \text{ kU}_A/\text{L}$ and the median post-chemotherapy level was $0.600 \text{ kU}_A/\text{L}$ ($p < 0.001$) (Fig. 1). The median pre:post-chemotherapy A-IgE ratio was 2.6 (range, 0.5–45.7). In 24 (67%) of the 36 patients, A-IgE levels remained in the atopic range, whereas in the remaining 12 (33%) patients, A-IgE levels declined into the nonatopic range (Fig. 1).

To determine whether the pre:post-chemotherapy A-IgE ratio is related to patient/treatment characteristics, we compared the ratios between males and females, older patients (>48 years, which was the median) versus younger patients, patients in whom the “pre-chemotherapy” specimen was drawn before the start of induction chemotherapy versus up to 7 days after the start, patients with lymphoid malignancies (ALL or Burkitt’s lymphoma) versus myeloid malignancies (acute myeloid leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, or myelodysplastic syndrome), patients who received ≥ 3 versus <3 chemotherapies between the pre- and post-chemotherapy blood sampling (3 was the median), and in patients in whom ≥ 1 chemotherapy cycle did versus did not contain a corticosteroid (as an anticancer agent, not just as an antiemetic) between the pre- and

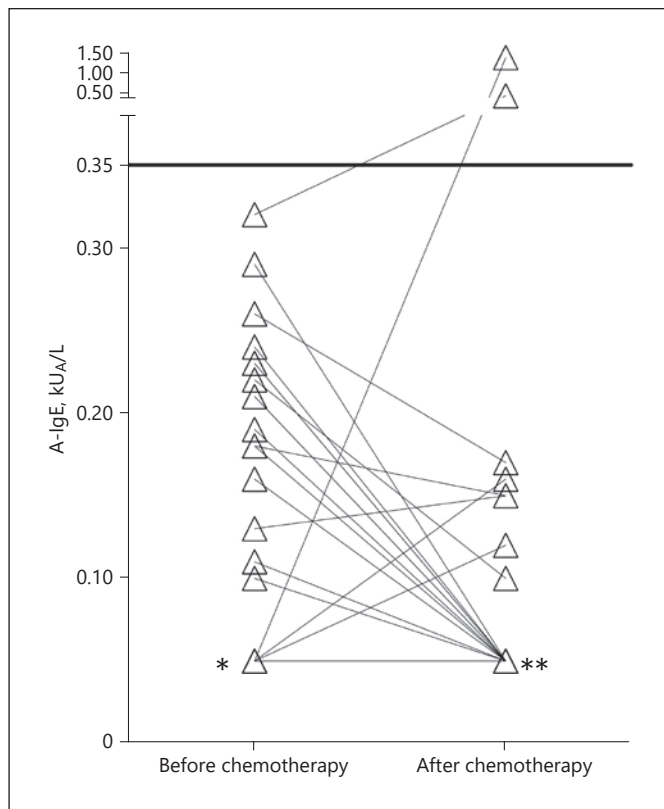


Fig. 2. Allergen-specific IgE (A-IgE) levels before and after chemotherapy in nonatopic patients ($n = 69$). The horizontal line indicates the cutoff ($0.35 \text{ kU}_A/\text{L}$) between the atopic and nonatopic range. As the lower limit of detection is approximately $0.1 \text{ kU}_A/\text{L}$, all values $<0.1 \text{ kU}_A/\text{L}$ are arbitrarily assigned a value of $0.05 \text{ kU}_A/\text{L}$. Asterisk denotes that the triangle showing the value of 0.05 represents 52 patients. Double asterisks denote that the triangle showing the value of 0.05 represents 60 patients.

post-chemotherapy blood sampling. There was no significant difference in the pre:post-chemotherapy ratios between any of these subgroups, with the exception of the subgroups of patients in whom chemotherapy did versus did not contain a corticosteroid (Table 2). For patients who received ≥ 1 cycle of chemotherapy containing a corticosteroid, the median pre:post-chemotherapy A-IgE ratio was 2.8; for patients in whom chemotherapy did not contain a corticosteroid, the median ratio was 1.75 ($p = 0.04$).

Given the influence of corticosteroids, we also analyzed A-IgE levels pre- and post-chemotherapy separately in atopic patients whose chemotherapy did or did not contain a corticosteroid. In the patients whose chemotherapy did not contain a corticosteroid ($n = 31$), A-IgE levels dropped from a median of 1.49 to 0.68 ($p < 0.001$).

Table 2. Comparison of pre/post-chemotherapy ratios of median allergen-specific IgE (A-IgE) levels between patient subgroups

Subgroups	A-IgE pre/post	<i>p</i> value
Age		
>48 years ($n = 48$)	1.46	0.056
≤ 48 years ($n = 57$)	2.00	
Sex		
Male ($n = 60$)	2.00	0.321
Female ($n = 45$)	1.67	
Diagnosis		
Lymphoid leukemia ($n = 19$)	2.60	0.078
Myeloid leukemia ($n = 83$)	1.75	
Chemotherapy ¹		
≥ 3 cycles ($n = 69$)	2.00	0.307
< 3 cycles ($n = 36$)	1.42	
Chemotherapy included a corticosteroid ²		
Yes ($n = 22$)	2.80	0.040
No ($n = 83$)	1.75	
Pre-chemotherapy blood sampling		
Before chemotherapy ($n = 88$)	2.50	0.454
≤ 7 days after chemotherapy ($n = 17$)	1.74	

¹ Number of chemotherapy cycles between the pre- and post-blood sampling.

² Discounting corticosteroids given purely as anti-emetics.

A-IgE became $<0.35 \text{ kU}_A/\text{L}$ in 9 (29%) of the 31 patients. In the patients whose chemotherapy contained a corticosteroid ($n = 5$), A-IgE levels dropped from a median of 3.22 to 0.34 ($p = 0.123$). A-IgE became $<0.35 \text{ kU}_A/\text{L}$ in 3 (60%) of the 5 patients.

Effect of Chemotherapy on A-IgE in Nonatopic Patients

Analogous to the atopic patients, A-IgE levels dropped in most of the nonatopic patients – the median pre-chemotherapy level was $0.04 \text{ kU}_A/\text{L}$ and the median post-chemotherapy level was $0.03 \text{ kU}_A/\text{L}$ ($p = 0.001$). The median pre:post-chemotherapy A-IgE ratio was 1.50 (range, 0.02–11.5); it was 1.20 among patients whose chemotherapy did not contain a corticosteroid and 1.83 among patients whose chemotherapy contained a corticosteroid. Thus, A-IgE levels generally remained in the nonatopic range (Fig. 2). The exceptions were 2 patients whose serum A-IgE concentrations increased to the atopic range; however, this was only to the low end of the atopic range ($0.42 \text{ kU}_A/\text{L}$ in 1 patient and $1.37 \text{ kU}_A/\text{L}$ in the other patient).

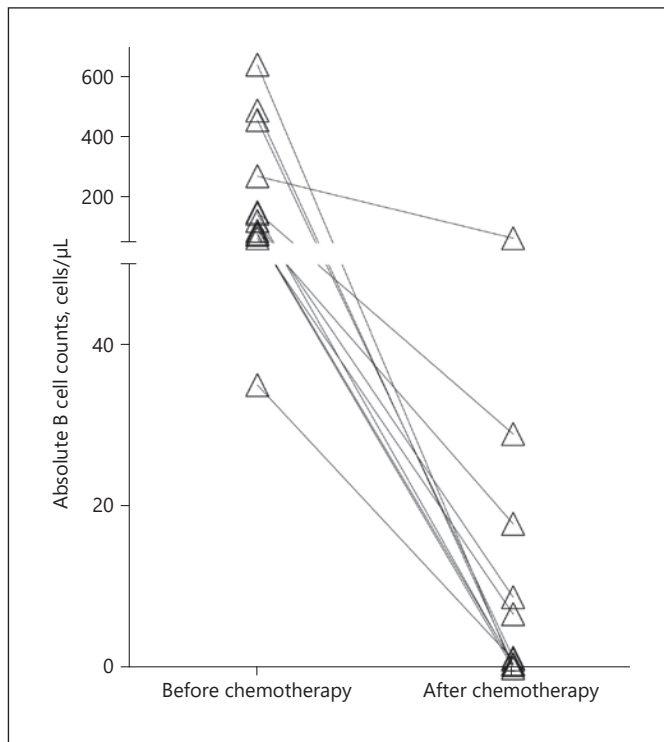


Fig. 3. Absolute blood B cell counts before and after chemotherapy ($n = 12$ patients).

Effect of Chemotherapy on B Cell Counts

The median absolute B cell counts were 135.6 cells/ μ L (range 35.1–644.2) before and 1.2 cells/ μ L (range 0.04–66.1) ($p < 0.001$) after chemotherapy (Fig. 3). The median ratio of pre:post-chemotherapy B cell counts was 87.6 (range, 4.1–14,641.0). Thus, the decline in B cell counts (median 87.6-fold) was substantially greater than the decline in A-IgE levels (median 2.6-fold among atopic patients, 1.5-fold among nonatopic patients, and 1.8-fold among total patients).

Effect of Chemotherapy on Total IgE

In atopic patients, total IgE levels declined after chemotherapy. Median total IgE levels were 144.7 kIU/L before chemotherapy and 29.7 kIU/L ($p < 0.0001$) after chemotherapy (Fig. 4). The median pre:post-chemotherapy A-IgE ratio was 3.2 (range 0.3–342.0).

In nonatopic patients, total IgE levels also declined after chemotherapy. Median total IgE levels were 20.7 kIU/L before chemotherapy and 6.9 kIU/L ($p < 0.0001$) after chemotherapy (Fig. 5). The median pre:post-chemotherapy A-IgE ratio was 2.6 (range 0.002–286.8).

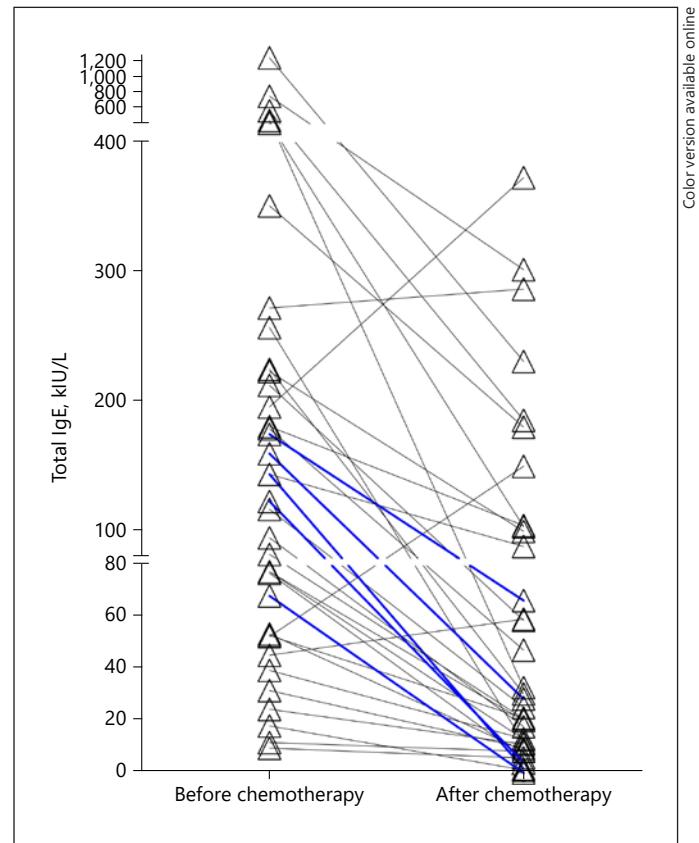


Fig. 4. Total IgE levels before and after chemotherapy in atopic patients ($n = 36$). Patients who received ≥ 1 cycle of chemotherapy containing a corticosteroid are indicated in blue. The lower limit of detection is approximately 0.2 kIU/L. Our clinical laboratory reference range is <0.2 to 160 kIU/L.

Discussion/Conclusion

Here, we showed that, contrary to our hypothesis that A-IgE levels would not decline after chemotherapy because A-IgE plasma cells are chemoresistant and long-lived, the levels did decline. However, this decline was relatively small; A-IgE levels declined only approximately 2-fold, whereas B cell counts declined approximately 88-fold. The 88-fold decline is probably an underestimate as we measured B cell counts a median of 48 days after the last chemotherapy, whereas in studies that measured B cell counts earlier after chemotherapy, B cells were barely detectable [15, 16]. This suggests that at least some A-IgE plasma cells survived after chemotherapy and continued to produce A-IgE even in the near absence of B cells.

One possible explanation for the small decline in A-IgE is the use of corticosteroids at high doses as part of

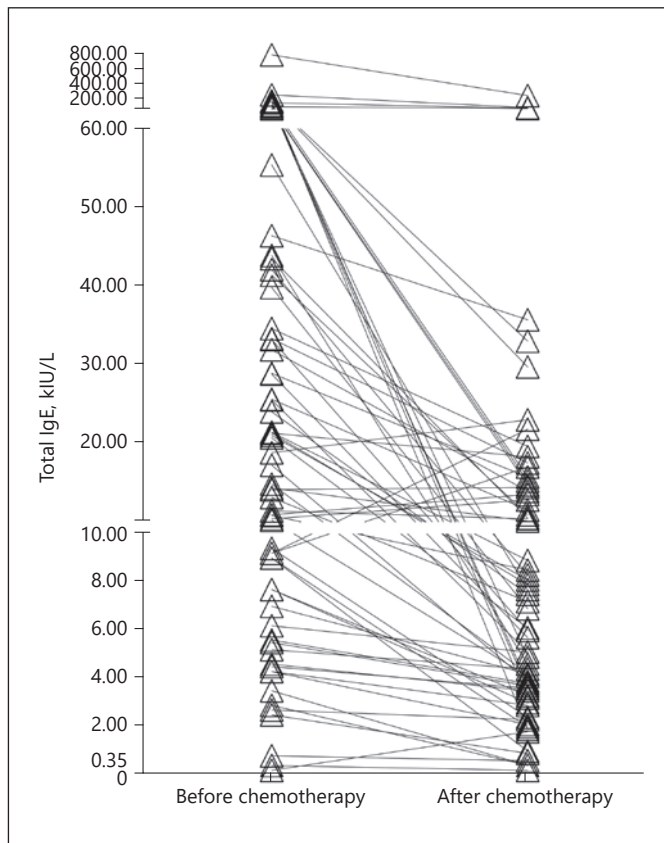


Fig. 5. Total IgE levels before and after chemotherapy in nonatopic patients ($n = 69$). The lower limit of detection is approximately 0.2 kIU/L. Our clinical lab reference range is <0.2 to 160 kIU/L.

chemotherapy (usually for ALL) or at low doses to prevent chemotherapy-induced nausea/vomiting, as corticosteroids can kill or inhibit plasma cells [17–20]. Consistent with that, we found a greater decline in A-IgE levels in patients whose chemotherapy did versus did not contain antineoplastic doses of corticosteroids. An alternative explanation for the small decline in A-IgE levels is that a small fraction of plasma cells is killed by chemotherapy or that chemotherapy partially inhibits the production of A-IgE. Yet another possible explanation is that A-IgE could be produced by both short- and long-lived plasma cells (both chemoresistant); the short-lived plasma cells would die by attrition during chemotherapy (not being replenished from B cells) and only the long-lived plasma cells persist. In rats, there is evidence for the existence of both short- (~3 days) and long-lived plasma cells [21]. Based on our data, we cannot conclusively determine which of the above explanations applies. However, given that A-IgE in atopic patients was still relatively high

48 days after the last chemotherapy cycle when B cell counts were very low, and given that the blood half-life of IgE is only 2–4 days [22], we can conclude that at least some A-IgE plasma cells are chemoresistant and survive for at least several weeks. A caveat of this conclusion is that chemotherapy may have reduced the number of mast cells [23, 24], which may have altered the IgE half-life.

Given that there is a mild decline in A-IgE with chemotherapy, there could be a decline in the severity of symptoms of allergic diseases like asthma, rhinitis, or eczema. We did not evaluate this. Jones et al. [25] and Weigel et al. [26] showed reduced asthma symptoms in children following chemotherapy. In those studies, A-IgE was not measured. Perhaps, the decreased asthma symptoms observed in their studies could be due at least in part to decreased A-IgE.

A potential limitation of our study is that we allowed patient blood to be drawn up to 7 days past the start of chemotherapy for the time point before chemotherapy. As the immunosuppressive effects of chemotherapy or corticosteroids could potentially cause A-IgE levels to transiently decline, we attempted to accrue patients prior to the start of treatment – but due to the short time interval between the diagnosis of acute leukemia and the start of chemotherapy, this was not always possible. However, there was not a significant difference in the pre:post-chemotherapy A-IgE ratios between the patients whose “pre-chemotherapy” blood was drawn before versus up to 7 days after the start of chemotherapy (Table 2). Thus, it is unlikely that the fact that the “pre-chemotherapy” specimen was in some patients obtained up to 7 days after starting chemotherapy influenced the conclusions of our study.

After autologous or allogeneic hematopoietic cell transplantation, which includes high-dose chemotherapy (“conditioning”), a rise in total IgE has been described [27, 28]. Contrary to that, we found that both A-IgE and total IgE declined after chemotherapy (without transplantation). This suggests that chemotherapy alone (without transplantation) does not result in increased IgE.

In summary, barring the above limitation, A-IgE level drops only slightly with chemotherapy, whereas B cell levels drop substantially. This suggests that, similar to IgG plasma cells, at least some A-IgE-plasma cells are chemoresistant.

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Statement of Ethics

All subjects provided their written informed consent. The study was performed according to the Declaration of Helsinki, and procedures were approved by the Conjoint Health Research Ethics Board of the University of Calgary (file No. REB15-0128).

Disclosure Statement

The authors have no conflicts of interest to declare.

References

- Verma R, Foster RE, Horgan K, Mounsey K, Nixon H, Smalle N, Hughes TA, Carter CR: Lymphocyte depletion and repopulation after chemotherapy for primary breast cancer. *Breast Cancer Res* 2016;18:10.
- Mackall CL, Fleisher TA, Brown MR, Magrath IT, Shad AT, Horowitz ME, Wexler LH, Adde MA, McClure LL, Gress RE: Lymphocyte depletion during treatment with intensive chemotherapy for cancer. *Blood* 1994;84:2221–2228.
- Kantar M, Cetingul N, Kansoy S, Kutukculer N, Aksu G: Immune deficiencies following cancer treatment in children. *J Trop Pediatr* 2003;49:286–290.
- Kurtenkov O, Klaamas K, Rittenhouse-Olson K, Vahter L, Sergejev B, Miljukhina L, Shljapnikova L: IgG immune response to tumor-associated carbohydrate antigens (TF, Tn, αGal) in patients with breast cancer: impact of neoadjuvant chemotherapy and relation to the survival. *Exp Oncol* 2005;27:136–140.
- Hammarlund E, Lewis MW, Hansen SG, Strelow LI, Nelson JA, Sexton GJ, Hanifin JM, Slifka MK: Duration of antiviral immunity after smallpox vaccination. *Nat Med* 2003;9:1131–1137.
- Yu X, Tsibane T, McGraw PA, House FS, Keefer CJ, Hicar MD, Tumpey TM, Pappas C, Perrone LA, Martinez O, Stevens J, Wilson IA, Aguilar PV, Altshuler EL, Basler CF, Crowe JE Jr: Neutralizing antibodies derived from the B cells of 1918 influenza pandemic survivors. *Nature* 2008;455:532–536.
- Holt PG, Sedgwick JD, O’Leary C, Kraska K, Leivers S: Long-lived IgE- and IgG-secreting cells in rodents manifesting persistent antibody responses. *Cell Immunol* 1984;89:281–289.
- Ndungu FM, Cadman ET, Coulcher J, Nduati E, Couper E, Macdonald DW, Ng D, Langhorne J: Functional memory B cells and long-lived plasma cells are generated after a single *Plasmodium chabaudi* infection in mice. *PLoS Pathog* 2009;5:e1000690.
- Luger EO, Fokuhl V, Wegmann M, Abram M, Tillack K, Achatz G, Manz RA, Worm M, Radbruch A, Renz H: Induction of long-lived allergen-specific plasma cells by mucosal allergen challenge. *J Allergy Clin Immunol* 2009;124:819–826.
- Mitre E, Nutman TB: IgE memory: persistence of antigen-specific IgE responses years after treatment of human filarial infections. *J Allergy Clin Immunol* 2006;117:939–945.
- Cooling LL, Sherbeck J, Mowers JC, Hagan SL: Development of red blood cell autoantibodies following treatment with checkpoint inhibitors: a new class of anti-neoplastic, immunotherapeutic agents associated with immune dysregulation. *Immunohematology* 2017;33:15–21.
- Beck KE, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, Kammula US, Topalian SL, Sherry RM, Kleiner D, Quezada M, Lowy I, Yellin M, Rosenberg SA, Yang JC: Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006;24:2283–2289.
- Janelins MC, Mustian KM, Palesh OG, Mohile SG, Peppone LJ, Sprod LK, Heckler CE, Roscoe JA, Katz AW, Williams JP, Morrow GR: Differential expression of cytokines in breast cancer patients receiving different chemotherapies: implications for cognitive impairment research. *Support Care Cancer* 2012;20:831–839.
- Heyd J, Donnenberg AD, Burns WH, Saral R, Santos GW: Immunoglobulin E levels following allogeneic, autologous, and syngeneic bone marrow transplantation: an indirect association between hyperproduction and acute graft-v-host disease in allogeneic BMT. *Blood* 1988;72:442–446.
- Rao A, Kelly M, Musselman M, Ramadas J, Wilson D, Grossman W, Shenoy S: Safety, efficacy, and immune reconstitution after rituximab therapy in pediatric patients with chronic or refractory hematologic autoimmune cytopenias. *Pediatr Blood Cancer* 2008;50:822–825.
- Zecca M, Nobili B, Ramenghi U, Perrotta S, Amendola G, Rosito P, Jankovic M, Pierani P, De Stefano P, Bonora MR, Locatelli F: Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. *Blood* 2003;101:3857–3861.
- Rhen T, Cidlowski JA: Antiinflammatory action of glucocorticoids – new mechanisms for old drugs. *N Engl J Med* 2005;353:1711–1723.
- Settipane GA, Pudupakkam RK, McGowan JH: Corticosteroid effect on immunoglobulins. *J Allergy Clin Immunol* 1978;62:162–166.
- Abdel Razik A, Shaheen A, Shaheen F: The effect of beclomethasone inhalation and oral montelukast sodium on serum IgE levels and clinical parameters in asthmatic children. *Al-exandria J Pediatr* 2005;19:341–346.
- Ohrui T, Funayama T, Sekizawa K, Yamaya M, Sasaki H: Effects of inhaled beclomethasone dipropionate on serum IgE levels and clinical symptoms in atopic asthma. *Clin Exp Allergy* 1999;29:357–361.
- Ho F, Lortan JE, MacLennan IC, Khan M: Distinct short-lived and long-lived antibody-producing cell populations. *Eur J Immunol* 1986;16:1297–1301.

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Author Contributions

S.W. wrote the manuscript. A.C. supervised the A-IgE determination. P.D.-K. enumerated B cells. M.M. and M.M. facilitated patient accrual and collection of specimens. C.L. provided technical assistance and assistance with data analysis. F.K. provided valuable input into the study design, analysis, or interpretation. J.S. designed the study, supervised the analyses, and edited the manuscript.

- 22 Dreskin SL, Goldsmith PK, Strober W: Metabolism of immunoglobulin E in patients with markedly elevated serum immunoglobulin E levels. *J Clin Invest* 1987;79:1764–1772.
- 23 Valent P, Blatt K, Eisenwort G, Herrmann H, Cerny-Reiterer S, Thalhammer R, Mullauer L, Hoermann G, Sadovnik I, Schwarzingger I, Sperr WR, Mannhalter C, Horny H-P: FLAG-induced remission in a patient with acute mast cell leukemia (MCL) exhibiting t(7;10) (q22;q26) and *KIT* D816H. *Leuk Res Rep* 2014;3:8–13.
- 24 Gotlib J, Berube C, Gowney JD, Chen CC, George TI, Williams C, Kajiguchi T, Ruan J, Lilleberg SL, Durocher JA, Lichy JH, Wang Y, Cohen PS, Arber DA, Heinrich MC, Neckers L, Galli SJ, Gilliland DG, Coutre SE: Activity of the tyrosine kinase inhibitor PKC412 in a patient with mast cell leukemia with the D816V *KIT* mutation. *Blood* 2005;106:2865–2870.
- 25 Jones PD, Henry RL, Francis L, Gibson PG: Chemotherapy reduces the prevalence of asthma symptoms in children with cancer: implications for the role of airway inflammation in asthma. *J Paediatr Child Health* 1999;35:269–271.
- 26 Weigel S, Schmidt SM, Bernig T, Mukodzi S, Beck JF, Ballke EH, Wiersbitzsky SK: Intensive chemotherapeutic regimens against acute leukemia transiently suppress asthma symptoms but do not lead to long-term relief. *Pediatr Hematol Oncol* 2000;17:659–665.
- 27 Geha RS, Rappaport JM, Twarog FJ, Parkman R, Rosen FS: Increased serum immunoglobulin E levels following allogeneic bone marrow transplantation. *J Allergy Clin Immunol* 1980;66:78–81.
- 28 Bengtsson M, Gordon J, Flores-Romo L, Cairns JA, Smedmyr B, Oberg G, Simonsson B, Totterman TH: B-cell reconstitution after autologous bone marrow transplantation: increase in serum CD23 (“IgE-binding factor”) precedes IgE and B-cell regeneration. *Blood* 1981;73:2139–2144.