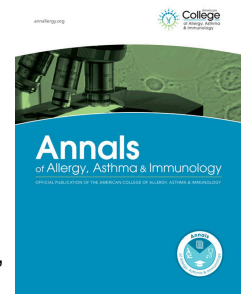


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EVALUATION OF HYPERSENSITIVITY REACTIONS TO CANCER CHEMOTHERAPEUTIC AGENTS IN PEDIATRIC PATIENTS

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**TITLE: EVALUATION OF HYPERSENSITIVITY REACTIONS TO CANCER
CHEMOTHERAPEUTIC AGENTS IN PEDIATRIC PATIENTS**

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Abbreviations:

ALL: Acute Lymphoblastic Leukemia

AML: Acute myeloid leukemia

FAAN: Food Allergy and Anaphylaxis Network

HL: Hodgkin's lymphoma

HRG: High-risk group

HSR: Hypersensitivity reaction

IDT: Intradermal test

LCH: Langerhans cell histiocytosis

NHL: Non-Hodgkin's lymphoma

NIAID: National Institutes of Allergy and Infectious Diseases

PEG: Polyethyleneglycol

SPT: Skin prick test

SRG: Standard-risk group

TRALL BFM: Turkish ALL-Berlin-Frankfurt-Münster

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Background: Hypersensitivity reactions(HSR) to chemotherapeutic agents have been increasingly documented.

Objective: The aim of this study was to investigate HSRs due to chemotherapeutics agents in childhood.

Methods: From January 2007 to June 2019, the patients who were treated for neoplastic diseases in our hospital were evaluated. Patients who developed a HSR to chemotherapeutic agent were included.

Results: Fifty-seven patients with 65 reactions (60% anaphylaxis) were evaluated. E.coli asparaginase was responsible for 58.5% (38/65) of these reactions. The other agents were polyethylenglycol(PEG)-asparaginase (n=11), etoposide (n=7), methotrexate (n=4), carboplatin (n=4), procarbazine (n=1). Of the 38 patients who had a reaction to E.coli- asparaginase, 33 patients received alternative treatment (PEGasparaginase or Erwinia asparaginase), 3 patients continued with desensitization, 2 patients underwent bone marrow transplantation. Five patients had an initial reaction to PEG-asparaginase, continued their treatment with Erwinia asparaginase or E.coli asparaginase uneventfully. Of seven patients who had a reaction to etoposide (4 had anaphylaxis), three patients continued with desensitization, 2 patients had the drug with premedication and prolonged infusion. Two patients had anaphylaxis with methotrexate. Treatment was continued with desensitization in one patient, methotrexate was discontinued in the other. Of the patients with carboplatin hypersensitivity (n=4), two had anaphylaxis. Desensitization was performed in two patients. One patient had procarbazine HSR, drug was given with premedication. **Conclusion:** Among all chemotherapeutic agents reviewed in our study which caused HSRs, asparaginase was the most co

INTRODUCTION

In the past decade, the use of chemotherapy for neoplastic disease has increased. Several hypersensitivity reactions (HSR) associated with the chemotherapeutic agents have been reported. Potentially, all chemotherapeutic agents can cause HSRs but generally, such reactions are significantly common when platinum compounds, taxanes, epipodophyllotoxins, procarbazine, and L-asparaginase are administered.^{1,2} HSRs may be related to the parent compound, their metabolites or the solvent.³ The mechanism responsible for most of these reactions are unknown. They may be immunologic or non- immunologic.^{2, 4} The clinical presentations can vary from mild cutaneous to severe life- threatening reactions.²

Diagnostic tests have a quite limited value in the diagnosis of chemotherapeutic HSR. Skin tests can be used in the evaluation of IgE-mediated chemotherapy reactions but standardized testing dose is only available for a minority of drugs. The lack of drug metabolites available for testing, unclear mechanisms responsible for reactions to certain drugs and possible toxicity of testing reagents restrict the use of skin tests.^{3, 5}

When a patient has a reaction with a chemotherapeutic drug, management options include using an alternative drug, giving the same drug with premedication or performing desensitization. Changing drugs can have a negative impact on patients' outcome when the culprit agent is essential or is the best treatment option. In these cases, drug desensitization is more convenient. The success of these options depends on the severity and the underlying mechanism of the HSR.^{3, 6}

Clinical data about HSRs induced by chemotherapeutic agents in the pediatric population is limited. The aim of this study was to investigate clinical features and management strategies of HSRs to chemotherapy in pediatric hematology/oncology patients.

METHODS

Patients

Medical records were reviewed retrospectively for patients who were diagnosed with malignancy and received chemotherapy treatment between January 2007 and June 2019 at the Hematology and Oncology Clinic of Ankara Pediatric Health and Diseases Hematology Oncology Training and Research Hospital. Our hospital receives pediatric patients from all over our country and a large number of hematology/oncology patients are treated every year with modalities including bone marrow and stem cell transplantation. Among patients screened, those who had developed HSRs to any chemotherapeutic agents were included in the study. For patients developing HSRs, the primary diagnosis, demographic data, causative chemotherapeutic drug, the chemotherapy protocol administered, the onset and timing of the reaction, symptoms and findings during the reaction and the method employed for the continuation of chemotherapy regimen following the reaction were recorded. Approval was obtained from the institutional ethics committee prior to initiation of the study.

Definition of Hypersensitivity and Anaphylaxis

The diagnosis of anaphylaxis was established according to the criteria defined in 2006 by the National Institutes of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN).⁷ Severity of anaphylaxis was classified according to the criteria suggested in the European Academy of Allergy and Clinical Immunology Taskforce on the management of anaphylaxis in childhood.⁸

Chemotherapy Protocols Employed

Diagnosis, chemotherapy drugs and chemotherapy protocols employed during the study are shown in the Table I. Patients with acute lymphoblastic leukemia (ALL) were

classified as being standard, medium and high risk of relapse based on the risk criteria of the chemotherapy protocols used for their treatment.

Diagnostic Allergy Work-up

Dilutions used for skin testing are shown in the table II.^{2, 5, 9, 10} Drugs were initially tested on volar forearm skin with the prick method, and reactions were considered positive when the diameter of the wheal is >3 mm greater than the negative control, with surrounding erythema, appeared within 20 minutes. When skin prick tests (SPTs) yielded negative results, 0.02 ml of the reagent solution was injected intradermally on the volar forearm skin. Readings were made 20 minutes after injections. Results were considered positive when an increase of >3 mm in the wheal diameter, accompanied by erythema, was present. Positive control assays for SPTs and intradermal tests (IDTs) were performed with histamine (10 mg/ml). As a negative control sample for both SPTs and IDTs, 0.9% NaCl was used.

Statistical Analyses

All analyses were performed using the SPSS Statistics for Windows, version 25.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics were expressed as mean $\pm$ SD or median (minimum-maximum) for continuous variables and as case numbers and percentage for nominal variables. The values were presented as medians and interquartile ranges (IQR) for the data that do not show a normal distribution.

RESULTS

Between January 2007 and June 2019, a total of 1005 patients received chemotherapy for hematologic oncologic malignancy at our institution. The diagnoses of the patients, the number of patients who received chemotherapy with these diagnoses and the number of patients who experienced HSR according to diagnoses are given in the table III.

During the study period, 57 patients with 65 reactions to chemotherapeutic agents were identified and evaluated. 58% were male (n=33), 77.2% (n=44) were diagnosed with ALL. Other diagnoses included infant ALL (n=1), acute myeloid leukemia (AML) (n=2), Hodgkin lymphoma (HL) (n=1), non Hodgkin lymphoma (NHL) (n=2), medulloblastoma (n=1), pilocytic astrocytoma (n=1), optic glioma (n=3), retinoblastoma (n=1), Langerhans cell histiocytosis (LCH) (n=1). The median age of patients was 7.2 years at the onset of HSRs (IQR 3.47-12.82). Diagnoses and chemotherapeutic agents related to the development of reactions are summarized in Table IV.

Among all reactions (n=65), 58.5% (n=38) were related to *E.coli* asparaginase. Other agents associated with HSRs were polyethyleneglycol (PEG) asparaginase (16.9%, n=11), *Erwinia* asparaginase (1.5%, n=1), etoposide (10.8%, n=7), methotrexate (4.6%, n=3), carboplatin (6.2%, n=4) and procarbazine (1.5%, n=1).

One patient had a reaction to all forms of l-asparaginase preparations (*E.coli* asparaginase, PEG-asparaginase and *Erwinia* asparaginase). 5 patients had reactions to both *E.coli* asparaginase and PEG-asparaginase. One patient had reaction with *E.coli* asparaginase, PEG-asparaginase and etoposide.

Of the reactions 60% were anaphylaxis. Number of anaphylaxis, signs and symptoms for each drug are detailed in Table V.

Reactions to asparaginase preparations

i) *E.coli* asparaginase HSRs

During the study period, a total of 406 patients were treated for ALL at our hospital. Among ALL patients, HSRs developed with *E.coli*-asparaginase in 38 patients (9.4%, 38/406) of whom median age at the onset of reactions was 6.67 (IQR 3.48-11.69) years and 63.2% (n=24) were male. One patient (2.6%) was in the low-risk, six patients (15.8%) were in the

medium-risk and 31 patients (81.6%) were in the high-risk group. Treatments were initiated according to the protocols given in table I.

Of the 38 reactions, 23.7% developed during the induction phase (n=9), 36.8% in the consolidation phase (n=14), 13.2% during the re-induction phase (n=5), 5.3% (n=2) in the maintenance phase and 21% (n=8) in the relapse stage. Of the reactions occurring under the ALL-IC-BFM protocol (n=25), 7 (28%) developed during the induction, 13 (52%) during the consolidation and 5 (15.8%) in the re-induction phase. The reactions induced by the St. Jude XIII protocol (n=5) included 2 reactions each developing in induction and maintenance phases and one during the consolidation phase.

In patients who were treated according to ALL-IC-BFM protocol, the reaction developed during median 10th overall lifetime dose (IQR 9-15). The earliest reaction to *E.coli* asparaginase occurred at the time of seventh dose of the drug in two patients and the latest reaction occurred at the time of 20th dose. Interestingly, 40% (n=10) of the reactions occurred at the 9th dose of *E.coli* asparaginase, which is the first asparaginase dose administered following the induction phase. Similarly, in relapsing patients, half of the reactions developed while administering the first 2 doses in the relapse phase (n=4).

Anaphylaxis accounted for 60.5% (n=23) of the reactions induced by *E.coli* asparaginase and 26.1% (n=6) of the anaphylaxis were evaluated as severe anaphylaxis. Of the anaphylaxis cases, 26.1% (n=6) developed in the induction phase, 13.1% (n=3) during the re-induction, 39.1% (n=9) in the consolidation and 21.7% (n=5) during the relapse phase (Figure 1). At the time of anaphylaxis, only nine patients were tested for tryptase and median tryptase value was 13.2 (IQR 3-21.2) μ l.

Of the patients, 89.5% (n=34) received the drugs via intravenous route and others intramuscularly. All reactions developed immediately. Anaphylaxis occurred in 64.7% (n = 22) of intravenous infusion and in only one patient taking the drug intramuscularly.

Only four patients underwent skin testing with *E.coli* asparaginase. One of these patients tested positive for the prick test and the other three patients tested positive for the intradermal test.

Among 38 patients, treatment was continued with *Erwinia*-asparaginase in 18 patients who did not have further reaction. For 15 patients, PEG-asparaginase were used. Reactions recurred in 6 of these patients (5 anaphylaxis); one received *E.coli*-asparaginase with desensitization and the remaining five patients were maintained on *Erwinia*-asparaginase treatment. Anaphylaxis developed in one of these 5 patients following the 8th dose of *Erwinia*-asparaginase and this patient could not receive the last dose of asparaginase. Three patients received *E.coli*-asparaginase with desensitization without further reaction. The desensitization protocols developed by Castells et al. were modified based on patient condition.¹¹ Two patients underwent bone marrow transplantation and did not require asparaginase treatment (Figure 2). The chemotherapy of the patient who could not take the last dose of asparaginase in protocol has been completed in March 2018, he is still in remission for the last 20 months.

ii) PEG-Asparaginase

Five patients developed an initial reaction to PEG-asparaginase (4 ALL, 1 infant leukemia) two of which had anaphylaxis. All ALL patients were in high risk group. In three patients, the reactions occurred while receiving their second doses of PEG-asparaginase. The other reactions occurred during the third and sixth doses of PEG-asparaginase by intravenous infusion in the relapse phase. Treatment was continued with *E.coli* asparaginase in one patient and with *Erwinia* asparaginase in 4 patients uneventfully.

Etoposide

During study period, 519 patients received etoposide. Seven patients had experienced HSR with etoposide and four had anaphylaxis. Etoposide was administered for AML in 2 patients and medulloblastoma, retinoblastoma, Langerhans cell histiocytosis, ALL, NHL; each in one patient. Etoposide preparation containing polysorbate 80 was used intravenously in our clinic and all reactions were observed during intravenous infusion of the drug. Two reactions developed at the time of the initial etoposide dosage. Reactions developed with the second dose in one patient, third dose in two patients, fourth dose in one patient and sixth dose in one patient.

Etoposide was given with hydroxyzine and methylprednisolone premedication and prolonged infusion in two patients uneventfully. Desensitization was performed with etoposide containing polysorbate 80 in three patients due to unavailability of etoposide phosphate and oral etoposide. Subsequent to premedication with hydroxyzine (1 mg/kg) and methylprednisolone (1 mg/kg), a 4-h protocol involving 12 steps and 3 solutions (solution A 0.002 mg/ml, solution B 0.02 mg/ml, solution C 0.2 mg/ml) was performed with no adverse events.¹² Oral etoposide could be supplied for one patient and was used without further reaction. Chemotherapy protocol did not include more etoposide doses in one patient and chemotherapy protocol was changed in another patient. That patient has completed his chemotherapy in August 2018 and his follow-up still continues regularly.

Carboplatin

A total of 151 patients received carboplatin for different types of malignancy during study period. Four patients developed HSR to carboplatin, two had anaphylaxis. Diagnoses were optic glioma (n=3) and pilocytic astrocytoma. All reactions occurred during intravenous infusion. Reactions developed with the 7th dose in two patients, 8th dose in one patient and

11th dose in one patient. SPT and IDT were performed in two patients. All skin tests were negative.

Subsequently, desensitization was performed using a 12-step protocol with 3 solutions (solution A 0.01 mg/ml, solution B 0.1 mg/ml, solution C 1.0 mg/ml) in 2 patients with no adverse events.¹¹ Carboplatin was discontinued in two patients. Treatment was continued with another chemotherapy protocol which did not include platinum compound in one patient and the other patient had his treatment with cisplatin without any problem. The treatment of the patients who received alternative drugs has been completed and their follow-up still continue for the last four years.

Metothrexate

During study period, 463 patients received methotrexate. Among patients developing HSRs to methotrexate (n=3), two had anaphylaxis and one had bullous erythema extending from the anterior aspect of the tibia to the ankle. Patients administered methotrexate intravenously. Two of these patients had ALL and the third patient had NHL. Skin prick testing to methotrexate was performed in one of the patients and gave a positive result (20x18 mm induration). Methotrexate was continued with premedication in the patient developing bullous erythema with no further reactions. In the second patient, methotrexate was administered with desensitization. Desensitization protocol developed by Oulego-Errez et al. was applied.¹³ According to this protocol, following the infusion of 1/1000 of total dose in 90 minutes, 1/100 of total dose infused at the same rate and then 1/10 of total dose infused in 6 hours. The rest of full dose was given in 18 hours. Chemotherapy was continued with alternative protocol (ifosfamide, carboplatin, etoposide) in the third patient. This patient was in the NHL high risk group, chemotherapy protocol was changed due to primary refractory disease and he died of central nervous system involvement, relapse under chemotherapy and progressive disease.

Procarbazine

Procarbazine was given to 33 patients during study period. Generalized maculopapular rash developed following 35th dose of procarbazine in a patient treated for HL. Further procarbazine doses were administered with hydroxyzine and methylprednisolone premedication. No reactions occurred thereafter.

DISCUSSION

During the study period, 57 patients showed HSR to the chemotherapeutic agents. Most of the reactions were of immediate type and developed with L-asparaginase. The most common reaction was anaphylaxis. Fifty two of 57 (91.2%) of the patients studied could take their planned doses. Four patients continued their treatment with alternative drugs or protocols. Only one patient couldn't take his last dose of asparaginase because he developed severe HSR to all forms of l-asparaginase and the last dose was not given with modification the protocol.

All chemotherapeutic agents are associated with potential HSRs but these reactions usually occur with platinum compounds, taxanes, epipodophyllotoxines, procarbazine and L-asparaginase.² Consistent with the literature, HSRs were more commonly reported with L-asparaginase, etoposide, methotrexate, carboplatin and procarbazine in the present study.

L-asparaginase is very immunogenic and often related with HSRs, the frequency in the pediatric population is reported up to 75.6%, depending on the route of administration and dosing.¹⁴ Although less than 10% of patients had severe anaphylactic reactions in previous

studies,⁶ severe anaphylaxis accounted for 15.8% of the reactions (26.1% of anaphylaxis) induced by *E.coli* asparaginase in our study.

L-asparaginase is one of the cornerstones in the treatment of ALL, patients who are given an insufficient course of asparaginase have been shown to have inferior outcomes. For this reason, management of asparaginase hypersensitivity is of utmost importance.¹⁵

There are three L-asparaginase preparations available for clinical use: an *Escherichia coli* derivative, an *Erwinia chrysanthemi* derivative and a PEG attached form.⁶ Asparaginase preparations derived from *E. coli* are the most widely used forms, most of the HSRs occur with this form. In this case, switching to a different preparation of L-asparaginase is an option to continue the therapy. By the use of different asparaginase preparations, therapeutic asparaginase activity can be achieved.^{6, 16, 17}

Erwinia asparaginase is antigenically different from *E.coli* asparaginase⁶ but allergic reactions to *Erwinia* asparaginase in children have also been reported in up to 37% of patients who continued their treatment with this preparation after clinical HSR to *E. coli* asparaginase.¹⁶⁻¹⁸ Although cross-reactivity has been reported after the first dose of *Erwinia* asparaginase, in this study, 18 patients were switched to *Erwinia* asparaginase and they could take their treatments without further reaction.

PEG-asparaginase is another less immunogenic option;⁶ HSR rate depends on the administration route. In one study, pooled hypersensitivity rates was found to be between 23.5% and 8.7% for IV and IM, respectively.¹⁹ But Burke et al reported that grade ≥ 3 HSR rates to PEG-asparaginase occurred less frequently with IV infusion than IM injection.²⁰ We have used PEG as an alternative for 15 of our patients and 6 had a reaction during infusion. Five of these reactions were anaphylaxis. Patients who developed an initial reaction to PEG-asparaginase had also HSR during IV infusion, two of them had anaphylaxis.

Soyer et al. reported that desensitization or premedication alone can be effective in managing systemic HSRs to *E.coli* asparaginase in children with ALL when there is no alternative asparaginase preparation available.²¹ Accordingly, desensitization was performed with *E.coli* asparaginase in 3 of our patients. However, in other studies^{22, 23} and consensus expert recommendations reported the formation of anti-asparaginase antibodies in many patients with hypersensitivity to *E.coli* asparaginase, resulting in subtherapeutic asparaginase activity. Therefore, use of premedication/ desensitization is not recommended.¹⁵

The risk factors for L-asparaginase HSR include IV infusion, repeated course of treatment, a time interval of ≥ 1 week between infusions, doses $>6,000$ IU /m²/d and single-agent chemotherapy.⁶ Consistently, 87.5% of our patients were given *E.coli* L-asparaginase via intravenous route. As a remarkable finding, a significant portion of the HSRs occurred at the time of initial dosing during the consolidation or re-induction phases where the time interval between the two L-asparaginase doses was 2 weeks or longer and half of the reactions occurring at the relapse stage were observed during the administration of the first two doses.

Etoposide podophyllotoxin is a topoisomerase II inhibitor, available both in intravenous and oral formulation. Intravenous etoposide is associated with a 34-51% rate of HSRs in children with ALL and HL.^{24, 25} HSRs are frequently related to the polysorbate 80 compound used in the IV formulation as a solvent but reactions to etoposide itself is also reported.²⁵⁻²⁷

In the literature, cases of etoposide hypersensitivity have been managed with premedication with antihistamines, corticosteroids and prolonged infusion time²⁵ or switching to etoposide phosphate.^{26, 28} Desensitization is another option to continue the therapy when etoposide phosphate is unavailable. In our hematology-oncology clinic, patients are given intravenous etoposide containing polysorbate 80. In the present study, we had six

patients with HSR to etoposide polysorbate. We could not give the drug with premedication and prolongation of the infusion in three patients so the patients were desensitized due to a shortage of etoposide phosphate.¹²

Procarbazine is an alkylating oral agent indicated for the treatment of HL, NHL, brain tumors and bronchogenic carcinoma. The incidence of HSRs ranges between 6% and 18%, but it is higher in patients with brain neoplasm who are receiving concurrent anticonvulsant therapy.²⁹ HSRs are common and include Gell and Coombs type I, III, and IV reactions.¹ There is no way to predict or prevent HSRs to procarbazine. It is generally recommended to discontinue the agent as symptoms are reported to recur at rechallenge¹ but our patient who developed a maculopapular rash was able to successfully complete his procarbazine after treatment with antihistamines and corticosteroids.

In our study, carboplatin-induced HSRs developed in patients treated for pilocytic astrocytoma and optic glioma. In the literature, carboplatin HSRs in the pediatric population have been reported in patients with low-grade glioma (LGG). The incidence of this reaction varies from 7 to 47% depending on the dosing schedule.³⁰⁻³² Carboplatin-associated reactions are usually mediated by IgE, are related to the cumulative number of infusions rather than the cumulative dose and reactions generally occur at the time of sixth cycle or later.^{3, 6} Studies in adults have shown a significant increase in the risk of carboplatin-induced HSRs after six cycles and remained high until the eighth cycle.^{33, 34} In our study, the reaction occurred at the time of seventh to eleventh carboplatin dosing. Skin testing performed after sixth or seventh carboplatin dose has been shown in adult studies to have a high negative predictive value (>98.5%) for patients at risk for carboplatin-related HSRs.^{35, 36} Appropriate options for the management include desensitization, the use of cisplatin instead of carboplatin or discontinuation of platinum therapy.⁶

284 Methotrexate, an antifolate metabolite, is widely used for the treatment of acute
285 leukemia and lymphoma. Discontinuation of methotrexate due to HSRs may critically reduce
286 the chances of successful treatment. Thus, desensitization protocols have been tested in many
287 cases.^{13, 37} In one of our patient with methotrexate HSR, we successfully performed the
288 desensitization protocol developed by Oulego-Errez et al.¹³

289 The strengths of our study include its conduct at a reference hospital with a large
290 population of pediatric hematology-oncology patients and a detailed review of HSRs to
291 chemotherapeutic agents in a pediatric population, which fills an important gap in the relevant
292 literature.

293 In conclusion, although all chemotherapeutic agents can cause HSRs, asparaginase is
294 the most common culprit in children. Reactions mostly involved anaphylaxis. When a HSR
295 develops, discontinuation of therapy may result in inferior outcomes but many of the patients
296 can take their planned doses by premedication, drug replacement or desensitization. Further
297 prospective studies involving larger samples are needed to collect more data on HSRs to
298 chemotherapeutic agents in pediatric population.

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TABLES

Table I. Diagnosis and chemotherapy protocol employed

Diagnosis	Protocols	Drugs
Acute lymphoblastic leukemia (ALL)	St Jude Total XIII protocol (Between 2007-2009)	Vincristine, cytarabine, methotrexate, daunorubicine, l-asparaginase, prednisone, cyclophosphamide, 6-mercaptopurine, doxorubicin, 6-thioguanine, ifosfamide, etoposide, vindesine, dexamethasone
	TRALL BFM protocol† (Between 2009-2012)	
	ALL-IC-BFM 2009 protocol‡ (Between 2012-2019)	
Relapsed ALL	REZ-BFM 2002 and 2009 protocol§:	Vincristine, cytarabine methotrexate, ifosfamide, l-asparaginase, 6-thioguanine, vindesine, daunorubicine, idarubicin, prednisone, cyclophosphamide, 6-mercaptopurine, dexamethasone
Acute myeloid leukemia (AML)	AML-BFM 2004 protocol	Cytarabine, idarubicin, etoposide, mitoxantrone, thioguanine, prednisone, methotrexate, daunorubicine, (ATRA:in promyelocytic leukemia)
Hodgkin lymphoma (HL)	ABVD-COPP	Doxorubicin, bleomycin, vinblastine, dacarbazine, cyclophosphamide, vincristine, procarbazine, prednisolone (etoposide)
non-Hodgkin's lymphoma (NHL)	BFM-NHL	Vincristine, doxorubicin, asparaginase, cytarabine, cyclophosphamide, prednisone, methotrexate, daunorubicine, 6-thioguanine, 6-mercaptopurine, dexamethazone
Medulloblastoma (MBL)	Baby POG* / CCNU, cisplatin, vincristine	Vincristine, cyclophosphamide, cis-platinum, etoposide, CCNU (lomustin)
Pilocytic astrocytoma (PA)		Carboplatin and Vincristine
Optic glioma (OG)		Carboplatin and Vincristine
Retinoblastoma (RBL)	VEC	Vincristine, Carboplatin, Etoposide
Langerhans cell histiocytosis (LCH)	DAL** HX 90 protocol / LCH III protocol	Prednisolone, vinblastine, etoposide and 6-mercaptopurine

† Turkish ALL-Berlin-Frankfurt-Münster

‡ Randomized Trial of the International Berlin-Frankfurt-Münster Study Group for the Management of Childhood Acute Lymphoblastic Leukemia

§ Protocol for the Treatment of Children with Relapsed Acute Lymphoblastic Leukemia

*Pediatric Oncology Group

**Deutsche Arbeitsgemeinschaft für Leukämieforschung

Table II. Dilutions used for skin testing

Chemotherapy agent	Skin prick test dilutions	Intradermal test dilutions
Asparaginase	Undiluted	20 U/ml
Etoposide	20 mg/ml	2 mg/ml
Carboplatin	10 mg/ml	1 mg/ml
Methotrexate	10 mg/ml	1 mg/ml, 10 mg/ml

Table III. Diagnoses and number of patients

Diagnoses	Number of patients	Patients with HSR
Leukemia		
<i>Acute lymphoblastic leukemia</i>	406	45
<i>Acute myeloid leukemia</i>	100	2
Lymphoma		
<i>Hodgkin lymphoma</i>	65	1
<i>Non Hodgkin lymphoma</i>	82	2
Brain tumors		
<i>Medulloblastoma</i>	33	1
<i>Astrocytoma (low+high grade)</i>	25	1
<i>Brainstem glioma</i>	11	-
<i>Ependymoma</i>	5	-
<i>Optic glioma</i>	6	3
<i>Other</i>	3	-
Neuroblastoma	67	
Wilms tumor	30	
Soft tissue sarcomas		
<i>Rhabdomyosarcoma</i>	26	
<i>Other soft tissue sarcoma</i>	4	
Neoplasms of bone		
<i>Osteosarcoma</i>	6	
<i>Ewing sarcoma</i>	14	
Retinoblastoma	15	1
Germ cell neoplasms	25	
Langerhans cell histiocytosis	28	1
Hemophagocytic lymphohistiocytosis	13	
Gastrointestinal neoplasm	5	
Neoplasms of the liver	13	
Rare tumors	23	

Table IV: Patient diagnosis and chemotherapeutic agents associated with reactions

	ALL	IL	AML	HL	NHL	MBL	PA	RBL	LCH	OG
E. coli asp (IV/IM)	38 (34/4)									
PEG-asp (IV)	10	1								
Erwinia asp (IV)	1									
Etoposide (IV)	1		2		1	1		1	1	
Methotrexate (IV)	2				1					
Carboplatin (IV)							1			3
Procarbazine (oral)				1						

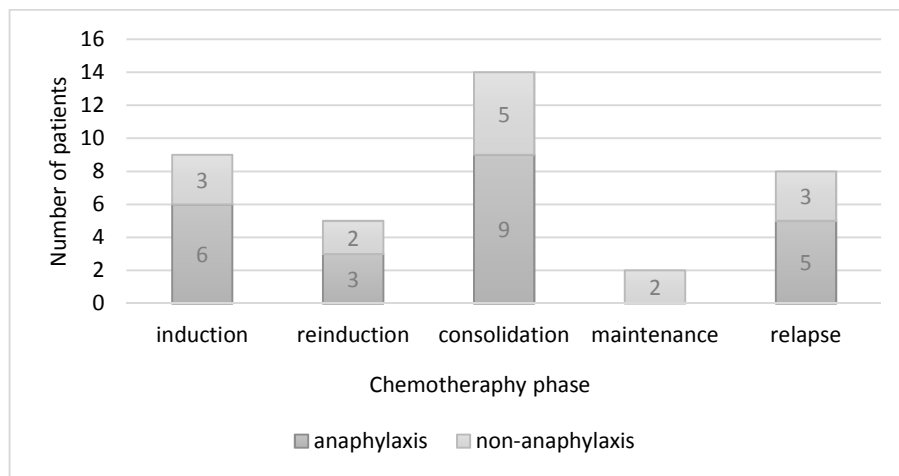
ALL: acute lymphoblastic leukemia, IL: infant acute lymphoblastic leukemia, AML: acute myeloid leukemia, HL: Hodgkin lymphoma, NHL: Non Hodgkin lymphoma MBL: medulloblastoma, PA: pilocytic astrocytoma, RBL: retinoblastoma, LCH: Langerhans cell histiocytosis, OG: optic glioma, Asp: asparaginase, PEG: polyethyleneglycol

Table V. Symptoms and signs during HSRs in 57 patients (total of 65 HSRs)

Symptoms and signs: no (%)	E.coli asp n=38	PEG-as n=11	Erwinia asp n=1	Etoposide n=7	Methotrexate n=3	Carboplatin n=4	Procarbazine n=1
Anaphylaxis	23 (60.5)	7 (63.6)	1 (100)	4 (57.1)	2 (66.7)	2 (50)	-
Cutaneous	36 (94.7)	9 (81.8)	1 (100)	5 (71.4)	3 (100)	4 (100)	1(100)
Urticaria	16 (42.1)	6 (54.5)	1 (100)			2 (50)	
Angioedema	18 (47.4)	3 (27.3)	1 (100)	3 (42.9)	2 (66.7)	1 (25)	
Flushing	6 (15.8)	1 (9.1)		1 (14.3)	1 (33.3)	2 (50)	
Pruritus	6 (15.8)			1 (14.3)	1 (33.3)	1 (25)	
Macular rash	2 (5.3)	1 (9.1)		1 (14.3)			1 (100)
Hyperemia	4 (10.5)						
Bullous erythema					1 (33.3)		
Respiratory	22 (57.9)	4 (36.4)	1 (100)	4 (57.1)	1 (33.3)	-	-
Dyspnea	17 (44.7)	3 (27.3)		4 (57.1)	1 (33.3)		
Cough	8 (21.1)	2 (18.2)	1 (100)				
Wheezing	5 (13.2)			2 (28.6)			
Nasal congestion/Rhinorrhea	2 (5.3)				1 (33.3)		
Hoarseness	2 (5.3)		1 (100)	1 ()			
Uvular edema	1 (2.6)		1 (100)	1 ()			
Laryngospasm	1 (2.6)						
Respiratory arrest	1 (2.6)						
Cyanosis	1 (2.6)			3			
Gastrointestinal	12 (31.6)	5 (45.5)	-	1 (14.3)	-	2 (50)	-
Abdominal pain	8 (21.1)			1		2 (50)	
Vomiting	8 (21.1)	4 (36.4)				1 (25)	
Nausea	2 (5.3)	3 (27.3)				1 (25)	
Diarrhea	2 (5.3)	1 (9.1)				1 (25)	
Difficulty in swallowing	2 (5.3)	1 (9.1)					
Cardiovascular	9 (23.7)	4 (36.4)	-	1 (14.3)	1 (33.3)	1 (25)	-
Hypotension	6 (15.8)	2 (18.2)		1	1 (33.3)	1 (25)	
Tachycardia	5 (13.2)	2 (18.2)					
Collapse	2 (5.3)						
Chest pain	2 (5.3)						
Neurological	2 (5.3)	1 (9.1)	-	-	-	-	-
Altered consciousness	2 (5.3)	1 (9.1)					
Other							
Fever	1 (2.6)						
Pallor	1 (2.6)	1 (9.1)					

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FIGURES

Figure 1: Anaphylactic vs non anaphylactic reactions by the chemotherapy phases**Figure 2. Management of the patients after HSR to *E.coli* asparaginase**