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Research Article

Frequency of Hypersensitivity Reactions to Chemotherapeutic Agents in Children with Cancer

Osman Ozturk,[1] Fazil Orhan[2]

[1]Department of Pediatrics, Bozok University Faculty of Medicine, Yozgat, Turkey
[2]Departments of Pediatric Allergy and Immunology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey

Abstract

Objectives: The aim of our study is to identify the frequency and the types of immediate hypersensitivity reactions that might be encountered during chemotherapy usage as well as which chemotherapeutics carry more risk of causing immediate hypersensitiviy reactions, to make the expactations of the units that perform chemotherapies more concrete for at least immediate hypersensitivity reactions and the precautions to be taken.

Methods: Sixty one patients with cancer who were hospitalised and treated in the pediatric oncology clinic. The number of total chemotherapeutic drug dosage, the number of total dosage for each chemotherapeutic drug, the number of total hypersensitivity reactions, the number of reactions against each chemotherapeutic agent,the frequency of common hypersensitivity reaction and the frequency of hypersensitivity reaction for each chemotherapeutic agent were calculated.

A total of 61 patients were followed. During the study period, 9 of 1992 chemotherapeutic dosages have been determined to cause immediate hypersensitivity reactions. Of the 61 patients followed during the study with the diagnosis of cancer, 8 developed hypersensitivity reaction.

Results: It has been determined that the frequency of immediate hypersensitivity reactions against chemotherapeutic drugs was quite low and severe, life-threatening type anaphylactic reactions were not present.

Conclusion: We found in the study group that the frequency of immediate hypersensitivity reactions to chemotherapeutic drugs was very low and no life-threatening severe anaphylactic reactions were found.

Keywords: Chemotherapeutic drugs, children with cancer, hypersensitivity

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An essential part of the diseases caused by drugs comprises of hypersensitivity reactions to drugs/drug allergies. The diagnosis of drug allergy is usually based on a history of unproven or suspected drug allergy given by patients. This, in turn, leads to false accusations of drugs and the use of less effective, more toxic, and more expensive drugs for the treatment of diseases. Physicians who encounter drug allergy in their patients usually misdiagnose them for fear of anaphylaxis although the patients do not have drug allergies. Drug allergies continue to intimidate doctors. Due to the limitations of diagnostic tests and the difficulty in evaluating these tests, many doctors prefer to ban the use of the drug instead of the diagnosis.

The present study aims to determine the frequency and type of immediate hypersensitivity reactions that may be encountered during the use of chemotherapy and determine which chemotherapeutics carry more risk to cause immediate hypersensitivity reactions, thus, to reveal the expectations of

Address for correspondence: Osman Ozturk, MD. Bozok Universitesi Tip Fakultesi, Pediatri Anabilim Dali, Yozgat, Turkey
Phone: +90 533 248 95 96 **E-mail:** epostosman@hotmail.com

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chemotherapeutic units in terms of immediate hypersensitivity reactions and to offer measures to be taken.

In our country, there is not enough study on the frequency of hypersensitivity reactions to chemotherapeutics in children with cancer. The present study will not only help to fill this gap for our country but will also create a database.

Methods

This is a prospective, single-center, observational study conducted between 1 May and 31 October 2010 with inpatients in the Pediatric Hematology-Oncology Unit, Department of Pediatrics, Faculty of Medicine, Karadeniz Technical University to determine the type and frequency of immediate hypersensitivity reactions to chemotherapeutics licensed by the Ministry of Health.

The immediate hypersensitivity reaction was defined as urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, and anaphylaxis occurring within the first hour after the last dose of the drug.[1]

Demographic characteristics (age, sex, type of cancer) of each patient were recorded. Total number of chemotherapeutic drug doses, the total number of doses for each chemotherapeutic drug, the total number of hypersensitivity reactions, number of reactions associated with each chemotherapeutic agent, the frequency of general hypersensitivity reactions (total number of reactions/total chemotherapy dose) and hypersensitivity reaction frequency for each chemotherapeutic agent (number of reactions/dose of chemotherapeutic agent) were calculated. Statistical analyses were performed with 95% confidence on the computer using SPSS 16.0 (Statistical Package for Social and Social) software. The results were presented as arithmetic mean (AO) +/- standard error (SE). Statistical significance was assessed by Chi-square test and $p<0.05$ was considered significant.

The study was approved by the Ethics Committee of Karadeniz Technical University with the report no: 06 dated 04.11.2010.

Results

A total of 61 patients (30 males, 49.1%, mean age 9.0±4.9 years) were followed up in the Pediatric Hematology-Oncology Unit throughout the study. Of the patients, 26 (42.6%) were in the 0-6 age range, 14 (22.9%) 7-12, and 21 (34.5%) were over 12 years of age. The most common type of cancer was acute lymphoblastic leukemia (ALL) (n=28, 45.9%), followed by medulloblastoma (n=7, 11.4%) and rhabdomyosarcoma (RMS) (n=5, 8.1%) (Table 1). During the study, acute adverse drug reactions developed in 25 (1.25%) of the 1992 dose chemotherapy regimens. Nine of them (0.4% in general, 36% in the reaction group, 9/25) developed as immediate hypersensitivity reactions. The chemotherapeutics that caused hypersensitivity reaction during use and the frequencies of IHR are presented in Table 2.

Table 1. Distribution of Patients by Age, Sex and Diagnosis

	n	%
Sex (Male/Female)	30/31	47.5/52.5
Age (years)		
0-6	26	42.6
7-12	12	19.7
>12	23	37.7
Diagnosis		
ALL	28	45.9
Medulloblastoma	7	11.4
RMS	5	8.1
HL	4	6.5
NHL	3	4.9
Neuroblastoma	3	4.9
AML	2	3.2
Ependymoma	2	3.2
Ewing	2	3.2
Other	5	8.7

Table 2. Chemotherapeutics that caused hypersensitivity reactions

Drug	Total Number of Doses	Number of IHR	Ratio of IHR
Cisplatin	24	2	8.3
L-asparaginase	65	5	7.6
Methotrexate	110	2	1.8
Adriamycin	64	0	0.0
Cyclophosphamide	34	0	0.0
Vincristine	49	0	0.0
ARA-C	155	0	0.0
Actinomycin-D	13	0	0.0
Mercaptopurine	854	0	0.0
Thioguanine	158	0	0.0
Idarubicin	21	0	0.0
Doxorubicin	49	0	0.0
Cyclosporine	96	0	0.0
Etoposide	74	0	0.0
Daunorubicin	64	0	0.0
Dacarbazine	13	0	0.0
Ifosfamide	22	0	0.0
Bleomycin	11	0	0.0
Uromitexan	99	0	0.0
Topotecan	14	0	0.0
Carboplatin	1	0	0.0
Mitoxantrone	2	0	0.0
Total	1992	9	0.4

IHR was mostly caused by cisplatin (in 2 of 24 cases, 8.3%), followed by L-asparaginase (5/65, 7.6%) and methotrexate (2/110, 1.8%). Throughout the study, of the 61 patients, a total of nine patients (13%) developed an immediate hypersensitivity reaction nine times. Of these patients, four were male (50%), and four were female (50%). Of these patients who developed IHR, seven (11%) were diagnosed with ALL and one (0.1%) with medulloblastoma.

The clinical features of hypersensitivity reactions in patients receiving chemotherapy are presented in Table 3. Of these reactions, three were followed by rhinitis, three with skin findings and three with anaphylaxis. Anaphylactic reactions were all mild. None of the three reactions resulted in an anaphylactic shock.

Discussion

This is the first prospective observational study to investigate the frequency of immediate hypersensitivity reactions to chemotherapeutic drugs in cancer patients followed in a Pediatric Hematology-Oncology Unit. Of the 1992 dose chemotherapeutic regimen in a six-month study period, 25 (1.25%) caused an acute adverse drug reaction. Nine of these reactions (generally 0.4%, 36% in the developing group, 9/25) were an immediate hypersensitivity reaction. An acute adverse drug reaction to eight of the 22 chemotherapeutic drugs was observed during this period. Immediate hypersensitivity reactions were caused by three of these eight drugs. These drugs were cisplatin (8.3%), L-asparaginase (7.6%) and methotrexate (1.8%), respectively.

Since there is no other research conducted with the method used in this study which investigated the frequency of immediate hypersensitivity reactions to chemotherapeutic drugs, it was not possible to compare the results with the literature. While no ratio is given, it is argued that hypersensitivity reactions to chemotherapeutic drugs contain only a small fraction of all adverse effects.[2] This judgment is based on the low frequency of hypersensitivity reactions reported by other studies investigating the frequency of adverse effects to drugs.[3] Gomes and Demoly report that the ratio of hypersensitivity reactions in all adverse drug reactions is about 1/3.[4] According to the results obtained from our study, this rate seems similar for all drug reactions caused acutely by chemotherapeutics. The rate of immediate hypersensitivity reactions in acute drug adverse effects observed during the present study was found to be 36%.

In our study, cisplatin caused the most hypersensitivity reactions (8.3%). Allergic reactions to cisplatin have been reported since its introduction in the 1970s. Different studies have reported allergic reaction rates to cisplatin in the range of 1-20%.[2,5] Severe anaphylactic cases in the administration of cisplatin have also been reported.[6] However, one of our cases developed mild anaphylactic reaction and the other developed rhinitis findings.

L-asparaginase is the chemotherapeutic drug with the highest risk of triggering immediate hypersensitivity reactions. Immediate hypersensitivity reactions are reported in 5-35% of patients.[7,8] Although the prevalence of immediate hypersensitivity to L-asparaginase in large series is reported as about 15%,[9] the risk of reaction is between 5% and 8% for each dose and may increase to 33% in the fourth dose.[7,9] Life-threatening anaphylactic reactions are less than 10%, and death is rare.[9] In contrast to the litera-

Table 3. Hypersensitivity reactions patients developed

Patient No	Age	Sex	Diagnosis	Drug	Adverse Effect	When did the Adverse Effect Occur?
I.	15	M	ALL	MTX	Fever, Runny nose	During infusion
II.	9	M	ALL	MTX	Nausea and vomiting, Runny nose, arthralgia-myalgia	During infusion
III.	3	M	ALL	L-Asp	Urticarial rash, sweating	At the fifth minute after injection
VI.	10	F	ALL	L-Asp	Urticarial rash, Nausea, and vomiting, Runny nose, arthralgia-myalgia	At the fifth minute after injection
V.	14	F	ALL	L-Asp	Urticarial rash, arthralgia-myalgia	At the first minute after injection
VI.	2	M	ALL	L-Asp	Urticarial rash, Runny nose	At the fifteenth minute after injection
VII.	7	F	ALL	L-Asp	Urticarial rash, arthralgia-myalgia	At the fifteenth minute after injection
VIII.	14	F	Medulloblastoma	Cisplatin	Nasal obstruction, Nausea, and vomiting	Within the first 2 hours after infusion
VIII.	14	F	Medulloblastoma	Cisplatin	Runny nose	During infusion

ture, L-asparaginase in our study group was found to be the second most common cause of immediate hypersensitivity reactions after cisplatin, and the rate of reaction was 7.6%. This can be attributed to the duration of the study, the route of administration, the number of doses and the differences between the patient groups. Dellenger[7] reported an immediate hypersensitivity reaction in 35% of 31 patients undergoing intravenous administration. Although Evans et al. could more accurately predict the frequency of an immediate hypersensitivity reaction due to L-asparaginase (14.8% in 245 children), the intravenous administration of the drug and the fact that only anaphylactoid reactions have been recorded instead of all immediate hypersensitivity reactions make it difficult to compare their results with our results. In our patients, the administration was by intramuscular route, and 4 of the reactions were a mild anaphylactic reaction, and one was urticarial rash.

Although immediate hypersensitivity reactions to methotrexate have been reported as case reports, there is no research on its frequency. However, immediate hypersensitivity reactions to methotrexate are considered to be rare. Reported immediate hypersensitivity reactions are urticaria, angioedema and anaphylactic reactions.[5] In our study group, two patients developed immediate hypersensitivity reactions due to methotrexate. One of these cases developed rhinitis, and the other developed a mild anaphylactic reaction.

No immediate hypersensitivity reaction was observed to other chemotherapeutic drugs used in children with cancer during the study period (Table 2). The reactions reported in the literature to most of these chemotherapeutic drugs which have not been reported to cause any hypersensitivity reactions have only been in the form of cases.[2,5] The frequency of hypersensitivity reactions to etoposide was reported to be 34% in a study with 108 ALL patients.[10] Hypersensitivity reactions to anthracyclines have been reported to be rare whereas the frequency of other side effects to pegylated liposomal doxorubicin is less than the frequency of hypersensitivity reactions, which is reported to be 9%.[11] Hypersensitivity reaction to mercaptopurine was reported as 2.7%[12] and to bleomycin as 1%.[13]

In conclusion, the frequency of immediate hypersensitivity reactions to chemotherapeutic drugs in the study group was very low, and no severe, life-threatening reactions were observed. No reaction was caused by chemotherapeutic drugs such as etoposide and doxorubicin which have been reported to cause hypersensitivity reactions in the literature. However, our results do not imply that these drugs do not carry the potential risk of severe hypersensitivity reactions. Each patient and each chemotherapeutic drug should be closely monitored in terms of hypersensitivity reactions.

Conclusion

This is the first prospective, observational study in the literature to determine the frequency of IHR to chemotherapeutic agents in children with cancer. Eight of 61 patients who were followed-up in the Pediatric Hematology-Oncology unit during a six-month study period developed immediate hypersensitivity reactions. An acute adverse drug reaction occurred in 25 (1.25%) of the 1992 dose chemotherapeutic regimens used during the study. Nine of them were IHR (0.4% in the whole group, 36% in the reaction group, 9/25). The drug that caused the most immediate hypersensitivity reactions was cisplatin (8.3%). L-asparaginase was found to be the second most common cause of immediate hypersensitivity reactions after cisplatin, and the frequency of reaction was 7.6%. It was found in the study group that the frequency of immediate hypersensitivity reactions to chemotherapeutic drugs was very low and no life-threatening severe anaphylactic reactions were found. However, this does not mean that drugs do not have the potential risk of causing hypersensitivity reactions. Each patient and each chemotherapeutic drug should be closely monitored in terms of hypersensitivity reactions.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Karadeniz Technical University with the report no: 06 dated 04.11.2010.

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