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Original Article

Acute Adverse Drug Reactions in Inpatient Children Diagnosed with Cancer over a 12-Year Period: A Report from a Single Center Study

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ABSTRACT

Objectives: In this study, we aimed to assess the incidence rate of adverse drug reactions (ADR) to chemotherapeutic agents and related problems in hospitalized pediatric patients diagnosed with cancer who referred to Mahak hospital in Tehran. **Methods:** All information about 125 children younger than 18-years-old who experienced ADR during their chemotherapy period (from March 2008 to March 2020) in Mahak Pediatric Cancer Treatment and Research Center (MPCTR) was collected and analyzed in SPSS-25. **Results:** Most of patients (approximately 65%, *n*=81) were male and the mean age of both genders was approximately 6.6 years of old. In addition, leukemia was the most common cancer type followed by Central Nervous System tumor. In terms of adverse events, skin and subcutaneous disorders occurred in 74 cases of 125, whereas nervous system, Immune system disorders and musculoskeletal related disorders were the least common events each occurring only in four cases. According to Naranjo's Probability Scale, most ADRs were evaluated as probable in relation with administrated drug (61.60%) and 56.80% of reactions were determined as mild. Furthermore, the commonest ADR-causative drugs were L-asparaginase followed by carboplatin (together more than 56% of all cases. **Conclusion:** The overall incidence of ADR amongst children diagnosed with cancer in our retrospective study was 3.68 %. Additionally, leukemia treatment regimen including L-asparaginase seems to be significantly vulnerable to induce ADRs in pediatric ward. Finally, there is a crucial need for monitoring pediatric patients during treatment process in order to reduce the risk of ADR occurrence.

Key words: Adverse drug reaction, Chemotherapy, Childhood cancer, Pediatrics, CTCAE.

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INTRODUCTION

Adverse drug reaction (ADR), "a response to a medicine which is noxious and unintended".[1,2] ADR incidence rate seems to have a higher rate in children who are hospitalized rather than those whose cause of hospital admission was ADR or other outpatient children.[3] Nearly 22% of hospitalizations considers to be as a result of ADR and 44.2% of ADRs may lead to hospital admission.[4] In a systematic review of ADRs in children, it was reported that ADR incidence might vary from 0.6% to 16.87% in hospitalized pediatric patients during their admission depending on their admission ward. It is also claimed that ADR incidence is significantly higher in studies in which a higher percentage of oncology patients are evaluated.[3]The chance of ADR caused by chemotherapeutic agents is significantly higher than normal drugs and this kind of injury may increase the rate of mortality, morbidity and long term sequelae amongst cancer patients.[5] In a cohort study of 1,000,000 children, it has been estimated that every child receives four prescriptions per year averagely, among whom nearly 25% accounts for more than 70% of drug usage. These children are considered to be those who developed complex malignancies such as cancer.[6] In our study, we aimed to evaluate ADR and related causes in pediatric patients diagnosed with cancer during their hospitalization in Mahak Pediatric Cancer Treatment and Research Center (MPCTR). Mahak hospital is a non-governmental organization (NGO) which support children with cancer and provide multimodality treatment and care for pediatric patients through Iran and even other countries. This is the first time in Iran that a study is designed to evaluate chemotherapy induced ADRs specifically for pediatric patients diagnosed with cancer. Therefore, our findings seem to be critical for healthcare providers in the field of childhood cancer to better understanding and monitoring of these unwanted events.

METHODS

Study design and patients

This cross-sectional study was designed and conducted on 125 children who experienced ADR during their hospitalization at Mahak Pediatric

Cancer Treatment and Research Center (MPCTR) amongst a total number of 4563 hospitalized patients from March 2008 to March 2020.

Inclusion and exclusion criteria

The inclusion criteria consisted of patients with rare and common malignancies who admitted for diagnosis and treatment modalities. Patients younger than 18 years of old at the time of ADR who received chemotherapy were included in our study (125 patients) and older patients, patients diagnosed with diseases except cancer and other outpatients were excluded from the study.

Data collection

To collect data, we designed a unique questionnaire, which was filled in by whether a pediatric hematologist-oncologist or the head nurse of the ward. Each questionnaire included patient's demographic information such as name, gender, date of birth, clinical data including type of cancer, start of ADR date, ADR duration, known drug allergies, drugs suspected for cause of ADR, clinical manifestation of ADR and drugs which were administered to suppress adverse reactions.

Severity, Probability and Preventability of reactions

To better understanding of the ADR levels and severity and the organ systems which were affected by these reactions, we used CTCAE criteria (Common Terminology Criteria for Adverse Events).[7] For determining the likelihood of whether the reported ADR is actually due to the administrated drug or the consequence of other factors, Naranjo's Probability Scale was utilized.[8] To be more precise, each ADR was reported based on system organ classification. If a patient's ADR to a certain drug was repeated in several times during the study period, only the first treatment was selected, although all of them were considered in Naranjo's scaling system. Table 1 explains more about these criteria and how to score the events based on it. For detecting whether any of ADRs were preventable or not, Schumock's questionnaire were filled out for each patient, which is shown in Figure 1.[9] ADR severity was also evaluated according to WHO classification of drug reactions and MPCTRC's treatment strategies. In favor of Hartwig's Severity Assessment Scale classification, an ADR that needs no change of suspected drug or requires discontinuation of it is called "a mild reaction and if the reaction needs not only drug discontinuation, but also an antidote which may lead to patient's hospitalization is called "a moderate reaction". Finally, "a severe reaction" is the event, which requires intensive medical care, harms the patient and may cause death.[10]

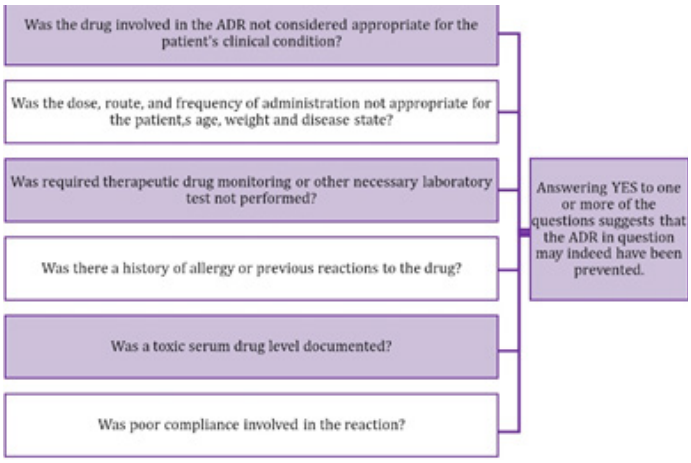

Figure 1: Schumock questionnaire for determining ADR preventability. If the answer to one or more of the questions above is "YES", the adverse drug reaction might have been preventable.[9]

Statistical Analysis

All of the collected data were entered in SPSS software version 25. Descriptive and *t*-test analysis were used for both parametric and non-parametric data.

RESULTS

Totally 125 eligible individuals out of 4563 admitted patients at MPCTRC enrolled in the study amongst whom, 35.20% (*n*=44) were female and 64.80% (*n*=81) were male (Male to female ratio:0.54).The mean age of patients at the time of diagnosis and ADR experience was 4.928±0.411 years and 6.656±0.442 years, respectively. The most common age range was 2 to 10 years (63.2%).

The commonest malignancy was leukemia (56.0%, *n*=70). The other diagnosed cancers in enrolled cases were CNS tumors (20.0%, *n*=25) and retinoblastoma (13.6%, *n*=17), respectively.

Details about the number of patients in each WHO-defined age groups, gender ratio, types of cancer and *MYCN* status are shown in Table 2.

The rate of ADR experience at MPCTRC from the whole of admitted cases was 2.73% of patients who recieved chemotherapy in our center. Adverse drug reactions were according to CTCAE are shown in Table 3. In this study, 307 adverse events were reported. The most problematic

Table 1: Naranjo Adverse Drug Reaction Probability Scale. The reaction is considered DEFINITE if the score is 9 or higher, PROBABLE if 5 to 8, POSSIBLE if 1 to 4, and DOUBTFUL if 0 or less.

Question	Yes	No	Not Known
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did adverse event appear after the suspected drug was given?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0
4. Did the adverse reaction appear when the drug was re-administered?	+2	-1	0
5. Are there alternative causes that could have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in any body fluid in toxic concentrations?	+1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Table 2: Demographic and clinical characteristics of pediatric patients (n=125).

	Leukemia	CNS tumors	Retinoblastoma	Lymphoma	Sarcoma	Neuroblastoma	Renal Tumors
Gender							
Female	21	11	5	2	3	1	1
Male	49	14	12	3	2	1	-
Age groups							
≤1 years	2	4	4	-	-	1	-
1-4 years	17	8	11	-	-	1	1
5-9 years	29	8	1	2	1	-	-
10-14 years	14	4	1	1	1	-	-
≥15	8	1	-	2	3	-	-
Mean Age (year)							
At the time of diagnosis	5.37±0.50	3.48±0.78	1.70±0.51	12.20±2.13	11.60±1.91	1.00±1.00	3.00±0.00
At the time of ADR	7.54±0.55	5.00±0.82	2.52±0.61	12.40±1.88	13.60±1.72	1.50±1.50	3.00±0.00

Table 3: System organs and related disorders caused by chemotherapy induced ADRs.

Organ system	Disorder
Skin and subcutaneous disorders (n=113)	Urticaria (n=45), Itching (n=25), Redness (n=30), Rash (n=9), Bullous dermatitis (n=4)
Respiratory system disorders (n=77)	Dyspnea (n=47), Cough (n=22), Tachypnoea (n=6), Apnea (n=1), Sore throat (n=1)
General system disorders (n=48)	Fever (n=15), Chills (n=9), Edema face (n=12), Malaise (n=9), Edema limbs (n=1), Flu-like symptoms (n=2)
Gastrointestinal disorders (n=25)	Abdominal pain (n=8), Diarrhoea (n=3), Nausea (n=9), vomitting (n=5)
Cardiac disorders (n=13)	Tachycardia (n=13)
Vascular disorders (n=10)	Hypertension (n=3), Superior vena cava syndrome (n=7)
Eye disorders (n=9)	Blurred vision (n=1), Photophobia (n=2), Edema eye (n=6)
Immune system disorders (n=4)	Anaphylaxis (n=4)
Nervous system disorders (n=4)	Headache (n=2), Seizure(n=2)
Musculoskeletal system (n=4)	Limb spasm (n=4)

adverse event (35.29%) was skin and subcutaneous disorders (113 event in total), while the least affected organ systems were nervous system (*n*=4), Immune system disorders (*n*=4) and musculoskletal system (*n*=4) with a rate of just a bit more than 1% of all ADRs. Furthermore, the most common reactions were dyspnea (*n*=47) and urticaria (*n*=45) and and the less common ones were apnea, sore throat, flu-like symptoms, Edema limbs and Blurred vision that each were observed just once (Table 3).

Based on Naranjo's Probability Scale, 61.60% of reactions (*n*=77) had a probable relation, 32.0% (*n*=40) had a definite relation and just over 6% (*n*=8) of events had a possible relation with the drug.

Patients experienced ADRs averagely 2.32±0.1 times (range from 1 to 6). In addition, none of ADRs were preventable based on Schumock questionaire. In terms of ADR severity level, 34.40% (*n*=41), 8.80% (*n*=11) and 56.80% (*n*=71) of cases were severe, moderate and mild, respectively.

The correlation between the drugs that were suspected to cause ADR and organ systems, which were affected by those drugs, are listed in Table 4.

Adverse reactions were significantly related to chemotherapeutic agents (80.8%, *n*=101), while only 19.2% of reactions were induced by non-chemotherapeutic agents (Table 5). L-asparaginase and carboplatin were the most commonly-used cytotoxic drugs which together were responsible for more than 56% of ADRs and causing nearly all types of organ system disorders, while metronidazole and voriconazole could be the less ADR-causative drugs effecting only gastrointestinal system and nervous system, respectively. Among non-chemotherapeutic ADR-causative agents (*n*=24), the commonest drugs were antimicrobials, which were responsible for 75.0% (*n*=18) of reactions related to this category. In addition, skin and subcutaneous was affected by a broad range of drugs including carboplatin, ceftriaxone, cyclophosphamide, cytarabin, ifosfamide, vancomycin, VP16, rituximab and L-asparaginase, whereas Immune system was affected only in case that L-asparaginase was administrated (Table 4). In terms of drug classification, the most adverse events were related to alkaloids and enzymes whereas the least problematic ones were anthracyclines and other rare drug groups (Table 5).

In all cases except eight, ADR lasted less than a day and the meantime between initiation of ADR and patients' complete improvement was 46.75 ± 7.86 min. Those eight patients whose adverse reactions lasted more than a day were diagnosed with leukemia (*n*=2) and CNS tumors (*n*=6). They also were under treatment with ceftriaxone and vinblastine and their ADR duration ranged from 25 hr to 10 days.

Totally, Hydrocortisone was prescribed for 61.45 % of patients to alleviate their adverse events followed by diphenhydramine (42.40%), oxygen therapy (27.20%), paracetamol (7.20%), promethazine (1.60%) and other drugs.

DISCUSSION

This study assessed the acute ADRs pattern amongst pediatric patients diagnosed with cancer during their hospitalization for receiving chemotherapy in Iran over a relatively long-term period. Although these types of reactions are not frequent in children in comparison with adults, chemotherapy-induced ADRs are the most common severe events in this age group. In our study, the incidence rate of ADR occurrence was 2.73%, while in a most recently studies, it was reported from 8.7% to

Table 4: The relation between drugs associated with ADRs and affected system organs.

	Amphotericin B	Carboplatin	Ceftriaxone	Cisplatin	Clofarabine	Cyclophosphamide	Cytarabin	Doxorubicin	Ifosfamide	IV-IG	L-ASP	Methotrexate	Metronidazole	Rituximab	Streptokinase	Vancomycin	Vinblastine	Vincristine	Voriconazole	Etopside (VP-16)
Skin and subcutaneous disorders	-	20	3	-	1	1	2	-	1	-	27	-	-	2	-	7	3	-	-	7
Respiratory system disorders	4	6	1	1	-	2	-	1	1	-	28	0	1	2	1	3	-	1	-	9
General system disorders	1	9	1	-	-	4	1	1	-	3	13	1	-	-	-	-	-	1	-	2
Gastrointestinal disorders	1	3	1	-	1	-	-	-	-	-	8	-	1	-	1	-	-	1	-	2
Cardiac disorders	1	1	1	-	-	-	-	1	-	-	6	1	-	-	-	1	-	-	-	1
Vascular disorders	1	-	1	-	-	-	-	-	-	1	5	-	-	-	1	1	-	-	-	-
Eye disorders	-	2	-	-	-	1	-	-	-	-	2	-	-	2	-	-	-	-	1	2
Immune system disorders	-	-	-	-	-	-	-	-	-	-	4	-	-	-	-	-	-	-	-	-
Nervous system disorders	-	1	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-	1	-
Musculoskeletal system disorders	2	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	1	-	-

Table 5: The relation between drug classifications associated with ADRs and affected system organs.

								Total	
	Enzyme	Alkaloid	Antimicrobial	Anthracycline	Antibody	Antimetabolite	Others	Chemotherapeutic Agents	Non-Chemotherapeautic Agents
Skin and subcutaneous disorders	27	32	10	-	2	3	-	61	13
Respiratory system disorders	28	21	9	1	2	-	1	50	12
General system disorders	13	16	2	1	3	2	0	32	5
Gastrointestinal disorders	8	6	3	-	-	1	1	14	5
Cardiac disorders	6	2	3	1	-	1	0	10	3
Vascular disorders	5	-	3	-	1	-	1	5	5
Eye disorders	2	5	1	-	-	-	-	7	1
Immune system disorders	4	-	-	-	-	-	-	4	0
Nervous system disorders	1	2	1	-	-		-	3	1
Musculoskeletal system disorders	-	1	2	1	-		-	2	2

16.2%.[11,12] It might be because of wider population including children with a broad range of disorders, not only the cancer-developed patients. Additionally, females' population of this study was smaller than that of males (with the ratio of 0.54), which was approximately similar to several other studies,[4,13,14] as well as patients' mean age (6.656±0.442 years) that can be supported by other studies.[15] Precisely, because of the fact that most of ADRs occurred in patients with leukemia and leukemia incidence is usually higher in 2-years to 10-years age group and male children are more likely to develop this kind of cancer, this age group and male patients form a significant portion of our patients.

In our study, each patient had experienced more than one ADR which was similar to other studies, while only 13.54% faced more than three adverse events, in contrast with most of other studies in which more than three ADRs was reported for nearly 80% of cases.[16] According to Naranjo's scale, most of reactions were probable due to drug usage, while 32.0% of reactions were definite, among which 57.5% (23 out of 40) were related to L-asparaginase utilization. It might be because of this matter that L-asparaginase was an inseparable part of routine treatment protocol for leukemia. Therefore, if an ADR happens any time after L-asparaginase administration, the score related to "reaction to previous exposure to the same drug (+1 score)" and the ones related to "reappearance of ADR after re-administration of suspected drug (+3 score)" were given and consequently, total score goes above nine (indicating a definite reaction).

In our study, mild reactions occurred in 56.80% patients. In another study in Malaysia, it is reported that 58% of patients experienced mild ADR, according to Hartwig's Severity Assessment Scale.[10,12] However, our severity level assessment was a little different, with regard to this fact that our study included old data from year 2008, when there was no accurate ADR-reporting system in our organization. Therefore, the severity assessment could be done based on adverse event manifestation and therapeutic strategies, nor based on a global ADR classification system.As same as a great number of other studies, the most ADR-causative drug was L-asparaginase (n=45). This seems to be because of this fact that more than 56% of patients were diagnosed with leukemia and L-asparaginase plays a vital role in treatment of this malignancy. Furthermore, all reactions related to L-asparaginase except two occurred after intravenous infusion of the drug. This kind of drug administration causes the most ADR since the drug enters directly into blood, which makes immune system more prone to react to the drug. This finding can be supported by other related studies.[14] Alkaloids including carboplatin, etoposide, ifosfamide and cyclophosphamide were the second top ranked ADR inducing drugs (n=49), since they are used in different regimens for treatment of a broad range of pediatric cancer malignancies.

Based on the present study, skin related disorders were the most frequent adverse event caused by chemotherapeutic agents followed by respiratory and general system disorders, because the skin disorder manifestations such as urticarial and itching could be the first noticeable changes of patient's body after a drug administration, as well as dyspnea (respiratory system disorder) and fever (general system disorder). This issue seems to be reported approximately the same in most of other chemotherapy-induced ADRs related studies.[4,14,15]There have been some limitations in our study due to poor ADR reporting system in the past. For instance, if a drug reaction was too mild, it would not be reported as an ADR, so its data was not available for analysis. Moreover, eight patients in our study experienced ADR that lasted more than one day. According to Table 5, all of them were diagnosed with either CNS tumor or leukemia and the majority of them were male children. Obviously, these two types of cancer were the most frequent. Furthermore, 75% of reactions were mild and vinblastine and ceftriaxone were the most ADR causative agents. Unfortunately, drug sensitivity tests had not been used for these children due to ignorance of its importance in the past. Since it was the first time in Iran that a study was specifically designed for evaluating drug reactions in children diagnosed with any type of cancer, we were unable to compare these findings with others.

CONCLUSION

Overall, it seems that pediatric patients who developed cancer are more likely to experience adverse drug events, because of their sensitive physical conditions and the characteristics of chemotherapeutic agents. The most common ADR stemmed from L-asparaginase, which was prescribed for treatment of the most frequent cancer type, leukemia. However, pharmacogenomics and evaluating sensitivity to a certain drug seem to be necessary regarding cancer patients' conditions. Although most of reactions were mild and controllable, there is a vital need for more accurate monitoring during treatment process as well as the need for evaluating probable reactions before prescribing the drug. Finally, we suggest that a similar but multicenter study being conducted in order to assess possible severe reactions in pediatric ward more reliable.

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Authors Contributions

Maryam Tashvighi: clinical studies; Yasaman Sadeghi: concepts, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquistition an analysis, statistical analysis, manuscript preparation and edditing, manuscript review; Narjes Mehrvar: design, data analysis, statistical analysis, manscript edditing and review; Mohammad Faranoush: concepts, clinical studies, manuscript review; Negin Jafariyan Lahijani and Mahyar Nourian: data acquistition; Mardawig Alebouyeh: clinical studies; Azim Mehrvar: clinical studies, manuscript review, guarantor.

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