Evaluation of Chemotherapy Toxicity in Acute Lymphoblastic and Myelogenous Leukemia

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Abstract

Background and Aims: Adverse drug reactions (ADRs) are one of the major leading causes of death in the world. This study was designed and conducted because of the importance of adverse events in the cancer treatment setting and regarding this issue there is no study exploring adverse reactions of acute hematologic malignancy chemotherapy in Iranian population.

Methods: This was a prospective, cross-sectional study performed at hematology-oncology and bone marrow transplantation research center. The inclusion criteria were all patients with acute hematologic malignancies such as **ALL** and **AML**, which were admitted over an 8 months period and were ≥15 years old age. Each ADR was categorized based on the WHO system organ classification.

Results and Conclusion: The total number of detected ADRs was 310 in total of 105 patients. Eight patients (7.6 %) experienced only one ADR, eleven patients (10.5%) experienced two ADRs and eighty-six of them (82%) experienced more than two ADRs. there was a significant relationship between the number of ADRs and type of hematologic malignancy. In this regard, the patients with AML malignancy showed more number of ADRs than with ALL malignancy ($p<0.05$) The Gastro-intestinal system disorders were the most common affected system-organ by chemotherapy regimens (33.5%). We suggest more well designed studies to determine the relation between the number of ADRs and study factors.

Key Words: ALL, AML, Chemotherapy, Adverse drug reactions, Toxicity

Introduction

Adverse drug reactions (ADRs) are the forth to sixth leading cause of death in the USA.(1, 2) Therefore detection, prevention and management of ADRs have become an important issue in the health systems. ADRs Induced by Chemotherapy agents, are one of the major complications of cancer therapy that affect the patients' survival and treatment outcomes and increase the morbidity and mortality rate. According to Australian National Hospital Morbidity Data about 11% of ADRs were related to antineoplastic and immunosuppressant drugs.(3) In the other study, antineoplastic agents were reported to be the most common drugs responsible for medication-related hospitalizations.(4)

Acute Lymphoblastic Leukemia (ALL) is the most common childhood cancer. In this setting, Vincristine, a Vinca alkaloid derivative plays the main role in remission-induction therapy regimen.(5) Its use is associated with an autonomic neuropathy and constipation.(5- 7)

Acute Myelogenous Leukemia (AML) is a hematologic malignancy affecting the myeloid line cells which is the most common acute leukemia in adults. Daunorubicin/Idarubicin and cytarabine are the standard induction chemotherapy for all types of AML, with one exception: acute promyelocytic

leukemia (APL) or FAB-M3.(8) In these context, all-trans-retinoic acid (ATRA), as the first line of therapy has significantly improved the outcome of disease.(8- 10) ATRA therapy can produce significant toxicities, including the peripheral neuropathy, retinoic acid syndrome (RAS), QT prolongation, and ALT/AST elevation.(10- 11)
Arsenic Trioxide (ATO), the other treatment option for APL, has been approved for remission induction and consolidation in patients with relapsed or refractory APL. ATO use induces significant adverse events such as QT prolongation, ALT/AST elevation and deep venous thrombosis (DVT).(12)
This study was designed and conducted because of the importance of detection, prevention and management of adverse events in the cancer treatment setting and regarding this issue there is no study exploring adverse events of acute hematologic malignancy chemotherapy in Iranian population. The aim of this study was to evaluate the frequency of ADRs induced by chemotherapy agents in the hospitalized patients with acute hematologic malignancies and to access the severity, causality and preventability of ADRs and to determine the impact of age, sex and other factors on the rate of ADRs.

Methods and materials

This was a prospective, cross-sectional study performed at hematology-oncology and bone marrow transplantation research center, Shariati teaching hospital, one of the major medical centers of Tehran University of Medical Sciences (TUMS). This study was approved in the ethic committee and all patients filled the consent form before entering the study. The inclusion criteria were all patients with acute hematologic malignancies such as **ALL** and **AML**, which were admitted over an 8 months period and were ≥15 years old age. Patients with the history of other diseases were excluded.
Based on the institution's protocols, all patients admitted with **ALL** received Vincristine (1 mg/m^2) on days one, eight, fifteen and twenty-two. Patients with all types of AML with exception of **AML-M3** received Cytarabine (100 mg/m^2/day) for seven days and Idarubicin (13 mg/m^2/day) for three days (7+3 regimen). Patients with **AML-M3** received ATO with doses of 0.15 mg/kg/day until bone marrow remission achieved (maximum: 60 doses). All the patients were monitored and recorded for chemotherapy induced ADRs.
Patients' Demographics, medical, drug and habitual history, chemotherapy regimen, telephone and Address were also recorded.

Table- 1. System-organs affected by chemotherapy induced ADRs.

system-organ classes	Frequency	Percent
Gastro-intestinal system disorders	104	33.5
Central & peripheral nervous system disorders	83	26.8
Respiratory system disorders	31	10
Musculo-skeletal system disorders	29	9.4
Skin and appendages disorders	16	5.2
Vision disorders	12	3.9
Platelet, bleeding & clotting disorders	11	3.5
Metabolic and nutritional disorders	7	2.3
Cardiovascular disorders, general	6	1.9
Psychiatric disorders	6	1.9
Urinary system disorders	5	1.6

Table 2. The most common system-organ involvements by chemotherapy regimens

system-organ classes	Regimen	Percent
Gastro-intestinal system disorders	ATO	14.2
Central & peripheral nervous system disorders	7+3	11.9
Respiratory system disorders	ATO	4.9
Musculo-skeletal system disorders	7+3	3.9
Skin and appendages disorders	7+3	2.9
Vision disorders	7+3	2.6
Platelet, bleeding & clotting disorders	All	1.3
Metabolic and nutritional disorders	Vincristine	1.3
Cardiovascular disorders, general	ATO	1.9
Psychiatric disorders	ATO	1.3
Urinary system disorders	7+3	1.6

ATO = arsenic trioxide; 7+3 = 7 days cytarabine + 3 days idarubicin regimen

Table- 3. The most common adverse reactions induced by chemotherapy regimens.

system-organ classes	Regimen	Adverse reaction
Gastro-intestinal system disorders	ATO	Nausea
Central & peripheral nervous system disorders	7+3	Fever
Respiratory system disorders	ATO	Cough
Musculo-skeletal system disorders	7+3	Back pain
Skin and appendages disorders	7+3	Rash
Vision disorders	7+3	Ocular pain
Platelet, bleeding & clotting disorders	All	Epistaxis
Metabolic and nutritional disorders	Vincristine	weight loss
Cardiovascular disorders, general	ATO	Edema
Psychiatric disorders	ATO	Insomnia
Urinary system disorders	7+3	Urine discoloration

ATO = arsenic trioxide; 7+3 = 7 days cytarabine + 3 days idarubicin regimen

According to the World Health Organization (WHO), ADRs are Defined as 'A noxious or unintended response to a drug, which occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease or for the modification of physiological function'. In this study, each ADR was categorized based on the

WHO system organ classification.(13) Causality assessment of ADRs was implemented according to the Naranjo's ADR probability scale.(14) Seriousness of detected ADRs was assessed based on WHOs definition. Preventability assessment was evaluated using Schumock *et al.* questionnaire.(15) Clinical pharmacist collected all the data, and coded for analysis in SPSS. Student's t-test and Mann-Whitney tests were used for two independent samples and **Kendall's rank** correlation and Kruskal–Willis tests were used to compare more than two independent samples. We also implemented chi-square test sand Ridge Regression. P values of less than 0.05 were considered statistically significant.

Results

During the 8-months study period, 105 patients, 66 males (63%) and 39 females (37%) met our inclusion criteria and entered the study.

The total number of detected ADRs was 310, which 196 of them was experienced by males and 114 of them by females. All of the patients experienced at least one ADR. Eight patients (7.6 %) experienced only one ADR, eleven patients (10.5%) experienced two ADRs and eighty-six of them (82%) experienced more than two ADRs.

Eventhought the most detected ADRs (60%) were occurred in the patients with BMI of 18-22 Kg/m^2 because more patients were included in this group of age, but patients with BMI of 28-32 Kg/m^2 experienced more number of ADRs. Most patients (28.5%) were in the range of 15-20 years-old and experienced most number of ADRs (26.5%).

According to the Naranjo's ADR probability scale, 26.1% of ADRs estimated as "possible" and 73.9% as "probable". The Gastro-intestinal system disorders were the most common affected system-organ by chemotherapy regimens (33.5%). the number and percentage of reported ADRs are shown in Table- 1.

In addition, the most common system-organ involvements by chemotherapy and the most common reported ADR of each organ-system are shown in table 2 and 3 respectively.

The chemotherapy regimens (7+3), ATO and vincristine were responsible for 39.0%, 36.8% and 24.2% of all ADRs, respectively.

As far as seriousness of ADRs, fourteen of detected ADRs (4.5%) were judged as serious. Seven of 105 patients (6.6 %) expired due to cancer complications. Not all ADRs were considered preventable according to Schumock questionnaire. The most common ADRs induced by chemotherapy regimens were fever (12.6%), nausea (9.7%), headache (8%), vomiting (7.7 %) and diarrhea (6.8%).

According to Mann-Whitney analysis, there was a significant relationship between the number of ADRs and type of hematologic malignancy. In this way, the patients with AML malignancy showed more number of ADRs than with ALL malignancy ($p<0.05$).

Based on analysis with Kruskal Wallis test, patients who were treated with (7+3) regimen and ATO significantly experienced more number of ADRs than vincristine regimen ($p<0.05$). In this study, we could not find any significant relationship between the number of ADRs and patients' age, gender, BMI, marital status, smoking habits, length of hospitalization, and concurrent use of drugs and history of other illness.

Discussion

ADRs are one of the major complications of drug therapy leading to morbidity and mortality as well as increasing the cost of therapy. Although, studies' findings generally exhibit similar patterns for identifying and decreasing of ADRs, there are usually differences between the incidences of ADRs detected with such studies. The definition of 'ADR', study population, genetic variation, sampling size, dosage and medications, race and other study factors may be responsible for these differences.

In our study, the average detected ADRs for each patient were three ADRs; whereas in Tierney *et al*. study on women with breast cancer, 5.4 ADRs per patient was reported.(16) These results may be due to the differences between the types of malignancy, chemotherapy regimens, gender, race, genetic and population. Most patients (81.9%) experienced more than two ADRs in our study, because chemotherapy agents are potential to induce adverse reactions.

Eventhough some studies have reported a significant relationship between the number of ADRs and patient's gender, age, race, and number of medications,(17, 18) but we could not detect such a significant relationship. This controversy may be the result of method, sample size and other study factors. Perhaps, better designed studies with larger sample size are able to describe these findings.

Gomez-Almaguer *et al*. reported that patients with malnutrition and low BMI exhibit more ADRs (19); however in our study, patients with BMI between 28 to 32 Kg/m^2 experienced more number of ADRs.

This finding may be describing the role of obesity and drug dosing in the frequency of ADRs. The number of ADRs with 7+3 regimen was more than other regimens. These results are in consistent with Bonneterre J *et al*. study that showed regimens containing anthracycline agents had more and serious ADRs than others without anthracycline agents.(20) Blood-related side effects of chemotherapy medications are their therapeutic effects in leukemia and are the most common ones; therefore, we did not recognize them as ADRs. In agreement with other studies, gastro-intestinal and central & peripheral nervous system disorders were the most common after blood side effects respectively.(21) According to Schumock questionnaire, all detected ADRs were non-preventable because of administration of chemotherapy regimens under the protocol and the life-threatening nature of malignancies.

The signs and symptoms of leukemia are the same as chemotherapy ADRs, the causality of most ADRs were classified as possible based on the Naranjo's ADR probability scale, accordingly.

The results of this study highlight the critical role of recognition, monitoring, detection, and prevention of ADRs in special malignancies and chemotherapy regimens to improve therapy outcomes.

As mentioned, in the setting of ADR studies, the definition of 'ADR', study population and patient orientation from ADRs and adherence, genetic variation, sampling size, dosage and medications, race and other study factors can affect the study result. This study has been affected also from these limitations. We suggest more well designed studies to determine the relation between the number of ADRs and study factors.

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