Adverse drug reactions of antineoplastic and immunomodulating agents reported to the Egyptian Pharmaceutical Vigilance Center

Original Article

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ABSTRACT

The aim of this study was to evaluate the pattern of Adverse Drug Reactions (ADRs) related to antineoplastic and immunomodulating agents in Egypt. We extracted all ADR reports of antineoplastic and immunomodulating agents (Anatomical Therapeutic Chemical (ATC) code L) that were reported to Egyptian Pharmaceutical Vigilance Center (EPVC) from January 2011 to December 2015 using VigiLyze TM. Afterwards, these reports were analyzed and categorized by age, sex, reporter qualification, seriousness, type of ADRs, medications, indications of use and causality. During the study period, 1905 reports related to antineoplastic and immunomodulating agents were received; 44.6% of which were reported by consumers and 56.8% by health care professionals. ADRs were serious in 13.3% and 65.1% of the cases reported by consumers and healthcare professionals, respectively. Approximately half (52.5%) of the reported ADRs occurred in females and only 8.4% occurred in children. Half of the reported ADRs (51.5%) occurred in middle aged group (45- 64 years). The most reported classes at the therapeutic level were immunostimulants (ATC code L03) and antineoplastic agents (ATC code L01). The most frequently reported medication was peg-interferon alfa-2a. The majority of ADRs were of the type "general disorders and administration site conditions" and "gastrointestinal disorders". In conclusion, ADRs caused by immunostimulants especially interferons have higher tendency to be reported in Egypt especially in the middle-aged group. Additionally, the study has shown that serious ADRs of antineoplastic and immunomodulating agents were more likely to be reported by healthcare professionals rather than consumers.

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1. INTRODUCTION

Adverse Drug Reactions (ADRs) are undesirable events resulting from taking a medication. The World Health Organization (WHO) defines ADR as any response to a drug which is noxious and unintended, and which occurs at doses normally used in human beings for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function[1]. In addition to their impact on population's health, ADRs possess a significant economic burden on healthcare system.

Antineoplastic and immunomodulating agents are used for treatment of different types of neoplasms and immune diseases[2]. High toxicity of these medications predispose patients to serious ADRs since the toxicity of anticancer medications is not limited to malignant cells but it can also affect normal cells[2].

The science of recognizing unidentified ADRs is called pharmacovigilance (PV). As defined by WHO, PV is the science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects or any other possible medication-related problems[3]. The scope of PV has also been expanded to include problems related to medication use like medication errors, off-label use, misuse and abuse[3]. The main purposes of PV are to ensure the safe use of medicines and to improve public safety[3].

Before any medication is launched to the market, it undergoes several phases of clinical trials to determine the safety and the efficacy of the drug[4]. However, these phases are usually not sufficient to detect all ADRs as clinical trials are conducted on a small number of patients for a short period with strict inclusion and exclusion criteria which excludes special populations like elderly people who already have a high prevalence of cancer diseases[4]. Consequently, this group is underrepresented in cancer clinical trials[4].

Spontaneous reporting is the main source of information for pharmacovigilance[5]. It is defined as voluntary submitting of ADR reports to national pharmacovigilance centers[5]. The main obstacle that confronts spontaneous reporting systems is under-reporting[5]. It causes delay in detecting ADRs and taking regulatory actions towards them[5]. Other limitations

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of spontaneous reporting include biases, delays in adverse events recognition and report quality[5].

United Kingdom took the lead in making voluntary reporting system when the Yellow Card was launched by Committee on Safety of Medicines (CSM) in 1964 after the thalidomide tragedy[6]. Yellow Card is a scheme for gathering information about Individual Case Safety Reports (ICSRs). The yellow card has been applied in many countries worldwide including Egypt.

Egypt joined the WHO Programme for International Drug Monitoring in 2001 but the Egyptian Pharmaceutical Vigilance Center (EPVC) has been established at the Central Administration of Pharmaceutical Affairs (CAPA) in December 2009[7]. The main role of EPVC is collecting reports submitted by physicians, pharmacists, other health care professionals and consumers using yellow cards as well as Council of International Organizations for Medical Sciences (CIOMs) forms submitted by Marketing Authorization Holders (MAHs)[8]. Yellow cards are available at EPVC website to be completed online or downloaded. They are also available at the pharmacovigilance coordinator in each hospital. Reports then can be received online, by fax, by e-mail, by hand or by phone.

The current study investigated the pattern of ADR reports on antineoplastic and immunomodulating agents received by EPVC during the first five years of its launching.

2. MATERIAL AND METHODS

This is a descriptive retrospective study that included all ADR reports related to antineoplastic and immunomodulating medications (Anatomical Therapeutic Chemical (ATC) code L) that were submitted to EPVC between January 2011 and December 2015. All spontaneous reports that complied with the validation criteria (identifiable patient, identifiable reporter, at least one ADR, at least one suspected drug) were collected. The study protocol was approved by the Ethics Committee of the Faculty of Pharmacy, Cairo University (Number of approval: CL (1330)).

Spontaneous reports were characterized according to the reporter qualification (physician, pharmacist, other healthcare professional or consumer), patient's age and sex, seriousness, ADRs classified by System Organ Class (SOC), medicines, indication of use and causality. Consumer is a person from general public who is not healthcare professional such as patient or patient's relative[9]. ADR data were extracted from VigiLyze TM which is a web-based search and retrieval tool that provides access to the global ICSR database (VigiBase) for all PV staff members[10].

Each ADR report contains only one case and one patient but it may be reported by one or more reporter and includes one or more ADR that is suspected to be caused by one or more drugs.

Regarding age, reports were classified into 5 groups as follow: 0-18 years old, 18-44 years old, 45-64 years old, 65-74 years old and more than 75 years old. This classification is based on the WHO classification and is already used by VigiLyze TM[11].

Serious ADRs were classified according to International Conference on Harmonization (ICH) definition into fatal, life-threatening, requiring hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability or incapacity, a congenital anomaly/birth defect and other medically important conditions[12].

Suspected medications were classified according to active ingredients using ATC classification up to the fourth level (chemical subgroup)[13]. Clinical manifestations were defined based on Medical Dictionary for Regulatory Activities (MedDRA) term using MedDRA Version 19.1 at SOC level[14].

Causality of ADRs was assessed using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) assessment scale into certain, probable/likely, possible, unlikely, conditional/unclassified or unassessable/unclassifiable[15].

3. STATISTICAL ANALYSIS

Data analysis was performed using SPSS version 22 (IBM Inc., Chicago, USA). Percentages and frequencies were calculated. Chi-square was used to test the association between the reporter qualification and the report's seriousness[16].

4. RESULTS

The EPVC received 7220 spontaneous ADR reports from 2011 to 2015, 1905 reports of which contained information about 5256 ADRs recorded for antineoplastic and immunomodulating drugs.

Based on the 2nd level ATC classification, medicines included in ADR reports were immunostimulants (ATC code L03) (47.2% of suspected drugs) followed by antineoplastic agents (ATC code L01) (43%), immunosuppressants (ATC code L04) (8.2%) and endocrine therapy (ATC code L02) (1.6%).

Regarding reporter's qualification, 44.6% of reports were received from consumers while 56.8% were reported by health care professional (33.2% physicians, 14.7% pharmacists and 8.9% other health care professionals).

Only 8.4% of ADR reports occurred in children (<18 years). Half of the reports were in older adults aged 45 to 64 years (51.5%) and 52.5% of ADR reports were reported for women.

Regarding seriousness, 43.3% of reports were serious including 112 fatal cases. Only 13.3% of reports submitted

by consumers were serious with 5 death reports while 65.1% of healthcare professional reports were serious with 101 death reports. This association between reporter's qualification and seriousness was statistically significant *(P< 0.05)*. Table 1 shows the correlation between reporter's qualification and seriousness of reports.

Table 1: Association between type of reporter and seriousness of reports received by Egyptian Pharmaceutical Vigilance Center (EPVC) from 2011 to 2015

Seriousness	Type of reporter		
	Healthcare professional	Consumer	*P-value (P<0.05)*
Death	100 (95.2%)	5(4.8%)	0.000
Life-threatening	85 (97.7%)	2 (2.3%)	0.000
Caused/prolonged hospitalization	191 (86.8%)	29 (13.2%)	0.000
Disabling/incapacitating	35 (97.2%)	1 (2.8%)	0.000
Congenital anomaly/birth defect	1 (100%)	0 (0%)	1.000*
Other	362 (81%)	85 (19%)	0.000
Not serious	333 (32.4%)	696 (67.6%)	0.000

* Fisher's Exact was used instead of Chi-square because one or more cells had expected count less than 5

Regarding fatal cases (n = 112), 60% were reported in males, 67% (n=75) were reported by physicians and only 4.4% (n= 5) were submitted by consumers. The incidence of fatal ADRs was highest common in the 45 to 64-year age group (30%, n=34). The most frequently reported fatal ADRs belonged to general disorders and administration site conditions (18.6%) followed by gastrointestinal disorders (10.2%) and blood and lymphatic system disorders (9.8%).

The majority of fatal reports were related to antineoplastic agents (L01) (75% of fatal reports) while immunostimulants (L03) caused death in 11.6% of fatal reports. Drugs associated with fatal reports were rituximab (ATC code L01XC02) (12.5%, n=14), sorafenib (ATC code L01XE05) (11.6%, n=13), doxorubicin (ATC code L01DB01) (10.7%, n=12) and docetaxel (ATC code L01CD02) (8.9%, n=10).

Peg-interferon alfa-2a (ATC code L03AB61) (n= 777) was the most frequently reported drug followed by interferon beta-1a (ATC code L03AB07) (n= 233), docetaxel (ATC code L01CD02) (n= 64) and rituximab (ATC code L01XX21) (n= 63).

Most of the reports related to immunostimulants were non-serious reports unlike reports related to antineoplastic agents which were serious in most of the cases (Table 2). Based on WHO-UMC causality assessment scale, most of ADRs (84.9%) were categorized as "possible". Only 0.5% were classified as "conditional/ unclassified" (Table 3).

Table 2: Distribution of adverse drug reactions reported to Egyptian Pharmaceutical Vigilance Center (EPVC) for antineoplastic and immunomodulating agents by medication and seriousness 2011 to 2015.

Therapeutic group (ATC)	Chemical/therapeutic/ pharmacological subgroup pharmacological subgroup	N (ADRs)	N (serious ADRs)
Antineoplastic agents (L01)	Nitrogen mustard analogues	66	47
	Other alkylating agents	12	9
	Folic acid analogues	47	42
	Purine analogues	22	18
	Pyrimidine analogues	154	117
	Vinca alkaloids and analogues	55	50
	Podophyllotoxin derivatives	10	6
	Taxanes	103	79
	Other plant alkaloids and natural products	2	2
	Actinomycines	10	9
	Anthracyclines and related substances	87	65
	Other cytotoxic antibiotics	7	4
	Platinum compounds	112	95
	Monoclonal Antibodies	122	79
	Protein kinase inhibitors	125	71
	Other antineoplastic agents	90	71
Total L01		1024	764
Endocrine therapy (L02)	Gonadotropin releasing hormone analogues	12	8
	Anti-estrogens	6	1
	Anti-androgens	4	0
	Aromatase inhibitors	16	8
Total L02		38	17
Immunostimulants (L03)	Colony stimulating factors	10	8
	Interferons	1107	240
	Other immunuostimulants	7	5
Total L03		1124	253
Immunosuppressants (L04)	Selective immunosuppressants	103	85
	Tumor necrosis factor alfa inhibitors	46	21
	Interleukin inhibitors	27	18
	Calcineurin inhibitors	10	8
	Other immunosuppressants	10	7
Total L04		196	139
Total L		2382	1173

Table 3: Causality of ADRs reported to Egyptian Pharmaceutical Vigilance Center (EPVC) for antineoplastic and immunomodulating agents: 2011 to 2015

Causality assessment	Percentage (%)
Certain	0.7%
Probable/likely	7.9%
Possible	84.9%
Unlikely	2.1%
Conditional/unclassified	0.5%
Unassessable/unclassifiable	3.9%

Hepatitis C Virus (HCV) accounted for 34.8% of the indications for suspected drugs (n=831) followed by multiple sclerosis (10%, n=240) and breast cancer (8.3%, n=197) (Table 4).

The most common ADR categories (according to MedDRA classification) were "General disorders and administration site conditions" (21.3% of ADRs), "gastrointestinal disorders"(11.4%) and "nervous system disorders" (10.6%) (Table 5). Based on reporter's qualification, the 2nd most common ADR category in consumers' reports was "gastrointestinal disorders". The

2nd most common categories according to physicians and pharmacists were "blood and lymphatic system disorders" and "nervous system disorders", respectively.

Table 4: Indications of antineoplastic and immunomodulating agents reported to Egyptian Pharmaceutical Vigilance Center (EPVC): 2011 to 2015

Indications	N (drugs)
Hepatitis C	831
Multiple sclerosis	240
Breast cancer	197
Hepatocellular carcinoma	100
Rheumatoid arthritis	47
Lung cancer	44
Non-Hodgkin's lymphoma	43
Colorectal cancer	37
Nodular lymphoma	33
Acute lymphoblastic leukemia	32
Soft tissue sarcoma	31
Bladder cancer	27
Colon cancer	23
Renal transplant	21
Lymphoblastic lymphoma	20
Other indications (n<20)	448
Unknown	208
Total drugs	2382

Table 5: Adverse drug reactions reported to Egyptian Pharmaceutical Vigilance Center (EPVC) for antineoplastic and immunomodulating agents: 2011 to 2015

Adverse drug reactions (SOC)	Frequency (%)
General disorders and administration site conditions	1117 (21.25)
Gastrointestinal disorders	597 (11.36)
Nervous system disorders	557 (10.6)
Investigations	383 (7.3)
Skin and subcutaneous tissue disorders	376 (7.15)
Blood and lymphatic system disorders	327 (6.22)
Musculoskeletal and connective tissue disorders	303 (5.76)
Respiratory thoracic and mediastinal disorders	268 (5.1)
Injury, poisoning and procedural complications	161 (3.06)
Psychiatric disorders	151 (2.87)
Vascular disorders	151 (2.87)
Infections and infestations	145 (2.76)
Metabolism and nutrition disorders	141 (2.68)
Immune system disorders	115 (2.19)
Eye disorders	108 (2.05)
Renal and urinary disorders	89 (1.69)
Cardiac disorders	59 (1.12)
Hepatobiliary disorders	52 (1)
Neoplasm benign malignant and unspecified	40 (0.76)
Reproductive system and breast disorders	34 (0.65)
Surgical and medical procedures	23 (0.44)
Ear and labyrinth disorders	20 (0.38)
Pregnancy puerperium and perinatal conditions	18 (0.34)
Endocrine disorders	10 (0.19)
Social circumstances	10 (0.19)
Congenital, familial and genetic disorders	1 (0.02)
Total ADRs	5256 (100)

DISCUSSION

To our knowledge, this is the first study to describe spontaneous ADR reporting in Egypt. We targeted reports of antineoplastic and immunomodulating medications as it was noticed that these drugs had the highest reporting rate in Egypt since establishment of EPVC till the end of 2015.

Based on previous studies, antineoplastic agents and immunomodulators are the most frequently associated medications with causing ADRs as most of drugs in this class have narrow therapeutic index[17]. It is well known that chemotherapeutic agents' mechanism of actions is dependent on their cytotoxic activity on rapidly proliferating cells[18]. Consequently, chemotherapy also possess toxicity towards normal tissues with high growth fraction like gastrointestinal tract, bone marrow and hair follicles[18].

Cancer is considered to be a major health problem in Egypt especially liver and breast cancer[19]. It is one of the most frequently leading causes of death worldwide and the third cause in Egypt[20]. Liver is one of the most common cancer sites in Egypt due to high prevalence of HCV as Egypt has the highest prevalence of HCV globally[19].

Our study identified the pattern of ADRs caused by antineoplastic and immunomodulating drugs reported to EPVC database. We found that the frequency of ADRs was higher in females than males. These results are consistent

with a European study done on antineoplastic and immunomodulators ADRs reported by consumers[21]. On the contrary, Whalang et al. showed in their study that ADRs are more common in male population[22]. The dominance of female reports can be explained by gender differences in the anatomical and physiological features such as fat composition and hormonal changes[23]. These differences might affect the pharmacokinetics and pharmacodynamics of medications[23]. Furthermore, female patients have higher drug utilization and medical consultation rates than males. High prevalence of breast cancer among Egyptian female patients may have contributed to their high reporting rate of antineoplastic ADRs[19].

The majority of ADRs were found in older adults (45-64 years) which is similar to what has been reported in a prior Bangladesh study. In that study, ADRs of antineoplastic medications mostly occurred in the age group (41-50 years)[24]. These findings could be attributed to the fact that this age group usually have multiple comorbidities such as diabetes, hypertension and other diseases which make them consume more medications and subsequently more prone to have ADRs.

Our study showed that consumers reported a large number of ADR reports for antineoplastic and immunomodulating agents (44.6%). This finding was surprising since PVC reporting in general is relatively new to Egypt. A British study in 2010 showed that low percent of antineoplastic and immunomodulating agents reports were reported by patients[25], even though Yellow Cards were introduce in the United Kingdom in 1964. This finding might be partially explained by the pattern of the EPVC awareness campaigns from 2011-2015. EPVC team has organized regular visits to hospitals to enhance the patients' awareness of PV using different educational tools such as posters and flyers. These tools have been distributed in the patients' waiting areas of different hospitals with different specialties. We found that oncology hospitals were among the top five hospitals that had PV awareness visits from 2011 to 2015. Further studies need to investigate consumer awareness of spontaneous reporting in Egypt.

A small percentage of consumer reports were considered serious. Similar results were observed by *Aagaard et al.*[21]. We found a statistically significant difference in the percentage of serious ADRs reported by consumers versus health care professionals. This could be explained by the fact that patients with serious ADRs would first seek the help of healthcare professionals whom then would initiate ADRs reporting rather than initiating a report themselves. In contrast, patients might report non-serious ADRs. Further analysis of non-serious ADRs is required since consumers and healthcare professionals may have different perception of seriousness[26].

Regarding causality, most ADRs were classified as possible with a low percentage of certain cases. This finding is similar to a study conducted by Joshi et al. which showed that the causality of most ADRs was possible with no certain ADRs[27]. Different results were found in other studies carried out in South India[28]. The most common causality assessment of ADRs in this study was probable followed by possible[28]. The small percentage of "certain" ADRs in our results is not surprising as the "certain" causal relationship between a medication and an ADR is difficult to establish, we have to get information about the incidence of ADR after reintroducing the medication "re-challenge"[15]. This is considered unethical and inapplicable in case of serious ADRs. As a result, lack of re-challenge information makes “possible” the utmost grade that can be assessed. Causality of some ADRs were "unassessable" due to insufficient or contradictory information collected about them.

In our study, general disorders and administration site conditions were the most commonly reported SOC from antineoplastic and immunomodulating drugs followed by gastrointestinal disorders and nervous system disorders and the most common ADR was fatigue. These findings are in concordance with what have been reported in previous studies. In a European study which was conducted on consumers' reports of antineoplastic and immunomodulating drugs, general disorders were the most frequently reported ADRs in the study population followed by skin and subcutaneous disorders and infections and infestations[21]. Another study conducted in an Indian hospital showed that gastrointestinal disorders was the most frequently reported SOC from antineoplastic medications followed by blood and lymphatic system disorders and the most common ADR was vomiting[29].

Immunostimulants were responsible for the majority of the ADRs especially peginterferon alfa-2a and Interferon beta-1a followed by antineoplastic agents and immunosuppressants. Conversely, immunosuppressants had the largest share in Aagaard et al. study followed by immunostimulants and antineoplastic agents[21]. In other study by *Schwartzberg et al.* immunosuppressants were observed also to be the most commonly reported class[30]. Previous studies have showed that Interferon beta has better safety profile than Interferon alpha in treatment of chronic hepatitis C[31]. This finding is in concordance with the use of peginterferon alfa-2a in Egypt.

Egypt has the highest HCV epidemic in the world. In 2015, in the less than 60-year age group, around 3.7 million Egyptian citizens had positive HCV RNA[32]. From 2007 to 2014, peginterferon and ribavirin were the standard of care for HCV in Egypt. More than 360,000 patients were treated with this regimen during this time period[33]. In our study, we found that patients treated for HCV had the highest reporting share of ADRs.

Among cancer patients in our study, breast cancer patients were the most common to experience ADRs. Breast cancer is the most frequent cancer in Egyptian female patients which explains our findings[19]. This is similar to a study conducted in a tertiary care hospital in South India to examine the adverse effects of anticancer

medications[34]. On the other hand, *Mallik et al.* showed that patients with lung cancer had the highest ADRs share in their study in a Nepalese hospital[35].

In spite that this study is the first to examine spontaneous ADR reporting in Egypt, the study had several limitations. First, this study was performed retrospectively therefore it was not possible to access the original reports and missing data was not recoverable. The fact that consumer reports were very high could not be explained nor investigated as well due to the retrospective nature. Second, underreporting is a major limitation making our results non-generalizable. One reason is that spontaneous reporting is relatively new to Egypt. In addition, many reasons have been suggested in the literature to explain under-reporting such as inability to recognize ADRs, lack of time, fear of responsibility and unawareness of reporting tools[5]. These reasons have been clarified in an Egyptian study to investigate under-reporting and the factors influencing ADR reporting[36].

5. CONCLUSION

In conclusion, ADRs caused by immunostimulants especially interferons have higher tendency to be reported in Egypt especially in the middle-aged group. Additionally, the study has shown that serious ADRs of antineoplastic and immunomodulating agents were more likely to be reported by healthcare professionals rather than consumers in Egypt.

Further prospective studies are needed to explore under-reporting of ADRs, ADR and automatic signal detection in Egypt and awareness of ADR reporting among consumers. The use of online reporting systems is suggested to save time and facilitate ADR reporting among healthcare professionals and consumers.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

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