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Analysis of Docetaxel Adverse Drug Reactions: A Retrospective Study Based on Iraqi Pharmacovigilance Center Database

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Abstract

Docetaxel is a chemotherapeutic agent approved for management of various cancers, but the occurrence of significant adverse drug reactions may affect the drug use and overall effectiveness in clinical practice. The purpose of the current study was to measure the distribution of adverse drug reactions of docetaxel reported in Iraq and to assess the causality, severity, seriousness, preventability, expectedness and outcome of these adverse reactions. A retrospective study conducted on individual case safety reports from the Iraqi Pharmacovigilance Center / Ministry of Health. The study included 118 individual case safety report containing 236 adverse drug reactions.

Most of the adverse drug reactions were related to "skin and subcutaneous tissue disorders" (26.7%), followed by "respiratory, thoracic and mediastinal disorders" (20.8%), "gastrointestinal disorders" (17.4%) and "general disorders and administration site conditions" (10.6%). The majority of these reactions with possible causality (68.6%), severity level 3 according to Hartwig's Severity Assessment (55.5%), expected (80.5%), possibly preventable (93.2%), and serious (80.5%). In addition, the most common outcome of adverse drug reactions was recovered / resolved (46.19%).

Keywords: Docetaxel, Pharmacovigilance, Adverse drug reactions, Iraqi pharmacovigilance center, Anti-Cancers.

تحليل التفاعلات الدوائية الضارة للدوسيتاكسيل: دراسة استرجاعية تستند إلى قاعدة بيانات مركز اليقظة الدوائية العراقي

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الخلاصة

دوسيتاكسيل هو علاج فعال ومعتمد لأنواع كثيرة من السرطانات ، لكن فعاليته في الممارسة السريرية يمكن أن تتأثر بحدوث تفاعلات دوائية ضارة. كان الهدف من الدراسة الحالية هو قياس توزيع التفاعلات الدوائية الضارة للدوسيتاكسيل المُبلغ عنها في العراق وتقييم السببية وشدتها وخطورتها والوقاية منها وتوقعها ونتائجها. هذه الدراسة هي دراسة بأثر رجعي أجريت على تقارير سلامة الحالات الفردية من مركز اليقظة الدوائي العراقي / وزارة الصحة. اشتملت الدراسة على ١١٨ تقريرًا فرديًا لسلامة الحالات يحتوي على ٢٣٦ تفاعلًا دوائيا ضارًا.

ارتبطت معظم التفاعلات الدوائية الضارة بالجلد واضطرابات الأنسجة تحت الجلد (٢٦,٧ ٪) ، تليها اضطرابات الجهاز التنفسي والصدر والمنصف (٢٠,٨ ٪) ، واضطرابات الجهاز الهضمي (١٧,٤ ٪) والاضطرابات العامة وحالات موقع الإعطاء (١٠,٦ ٪). غالبية التفاعلات الدوائية الضارة هذه كانت ذات سببية محتملة (٦٨,٦ ٪) ، وشدة معتدلة (٧٥,٤ ٪) ، ومتوقعة (٨٠,٥ ٪) ، وربما يمكن الوقاية منها (٩٣,٢ ٪) ، وخطيرة (٨٠,٥ ٪). بالإضافة إلى ذلك كانت النتيجة الاكثر شيوعا للتفاعلات الضارة هي التعافي منها او حلها (٤٦,١٩%).

الكلمات المفتاحية: دوسيتاكسيل ، اليقظة الدوائية ، التفاعلات الدوائية الضارة ، مركز اليقظة الدوائية العراقي ، مضادات السرطان.

Introduction

According to the World Health Organization (WHO), "pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem"[(1)]. Pharmacovigilance is a combination of communication systems, registries, and databases in a complex structure For a patient using a drug, pharmacovigilance represent an essential tool for the early identification of risk signals faced by the patient due to drug usage[(2)]. the main steps in the pharmacovigilance process is the identification and reporting spontaneously the (ADRs) which happened throughout the treatment, the process of pharmacovigilance should be applied carefully and continuously so that it can achieve its target which is the optimum safety of drug and in order to achieve this target the entire health care professionals should participate in the pharmacovigilance process also patients should be involved in the process through continuous patient education[(3)].

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As defined by WHO, the ADR is "any noxious or unintended response to a drug, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function"[4]. ADRs constitute a burden on the health care system because ADRs are a major cause of morbidity, hospital admission, increasing health care cost, and even increasing mortality rates[5]. The increase in the cost represent a huge burden on the health care system, health care facilities may spend 20% of their budget to deal with the complications encountered due to drug usage in some countries[6].

Cancer represent a major cause of mortality and morbidity with a yearly mortality rate of 12% worldwide[7]. Chemotherapeutic regimens are complex approaches for the treatment of cancer and patients with cancer are generally more prone to adverse drug reactions due to their decreased immune system function compared to normal individuals or patients of other disease areas[8].

Docetaxel is an important antimicrotubule agent from the family of Taxane's. It is a paclitaxel semisynthetic derivative of but it is more potent, derived from extracts of the leaves of the European yew tree (Taxus baccata), was discovered in the 1980's[9]. Docetaxel is highly effective when used as single therapy or in combination with other anti-cancer drugs for a number of cancers including breast cancer in different stages, head and neck cancers, gastric cancer, non-small cell lung cancer and androgen-independent metastatic prostate cancer[10]. Treatment regimens that contain docetaxel produce better outcomes in the metastatic, adjuvant, and neoadjuvant settings[11]. According to the summary of product characteristics (SmPC) by European Medicines Agency (EMA), "the most commonly reported adverse reactions of docetaxel alone are: neutropenia, anemia, alopecia, nausea, vomiting, stomatitis, diarrhea and asthenia. The severity of adverse events of docetaxel may be increased when docetaxel is given in combination with other chemotherapeutic agents"[12]. ADRs associated with docetaxel may cause stopping of treatment process, interruption of treatment process or may cause the dose of the drug being used to be decreased and thus affecting the treatment process. In some cases if the ADRs are not effectively treated the encountered risk may outweighs the potential benefit of docetaxel but results from clinical trials showed that when ADRs are managed effectively the quality of life and survival are greatly improved by docetaxel[13].

The aim of the present study was to demonstrate the distribution of docetaxel ADRs reported to the pharmacovigilance center and to analyze the causality, severity, seriousness, preventability, expectedness and outcome of these ADRs.

Subjects and Method

A retrospective study conducted on individual case safety reports (ICSR) obtained from the Iraqi Pharmacovigilance Center / Ministry of Health. The reports were collected via Vigiflow – Iraq. Vigiflow is provided by Uppsala Monitoring Center (UMC) which is a WHO collaborating center for adverse drug reactions from many national centers.

The study included 118 individual case safety report containing 236 adverse drug reaction which were analyzed for demographic distribution, ADR classification, causality, severity, expectedness, preventability and seriousness.

Adverse drug reactions were classified by the System Organ Classification (SOC) (Groups of adverse reaction pertaining to the same system-organ), and also classified according to the Preferred Term (PT) (Principal terms used for describing drug adverse reactions) according to the medical dictionary for drug regulatory affairs (MedDRA)[14]. The ADRs in PT was sorted in tables according to their SOC distribution to show count and percentage of the reported ADRs.

Causality was assessed using WHO-UMC criteria and were categorized into certain, probable, possible, unlikely, unclassified, and unclassifiable (table 1) [15].

Table 1. The WHO-UMC criteria for causality assessment [15].

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pathologically, pharmacologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

To assess the severity of the adverse events, the modified Hartwig and Seigel criteria have been used (table 2) [16].

Table 2. Hartwig's Severity Assessment [16].

Level of severity	The criteria
Level 1	An ADR occurred but required no change in the treatment with the suspected drug
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/ OR An Antidote or other treatment was required. No increase in LOS
Level 4	Any Level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission
Level 5	Any Level 4 ADR which requires intensive medical care
Level 6	The adverse reaction caused permanent harm to the patient
Level 7	The adverse reaction either directly or indirectly led to the death of the patient 2

Expectedness analysis was based on the Summary of Product Characteristics (SmPC) for each drug which is approved during the marketing authorization, each reported ADR was reviewed to check if it is included in the SmPC or not, if the ADR is included in the SmPC then the ADR is considered an expected ADR, if the reported ADR was not mentioned in the SmPC then the ADR is considered unexpected [17].

The preventability assessment was based on the modified Schumock and Thornton criteria where the ADRs were either preventable or non-preventable. If there was missing data making it not possible to answer all questions very clearly then the ADR is possibly preventable (table 3)[18, 19].

Table 3. Schumock and Thornton preventability assessment criteria[18,19]**.**

	Question	Yes	No
1	Was there a history of allergy or previous reaction to the drug?		
2	Was the drug involved inappropriate for patient's Clinical Condition?		
3	Was the dose, route, or frequency of administration inappropriate for the patient's age, weight or disease?		
4	Was there any required therapeutic drug monitoring, or other laboratory tests not performed?		
5	Was a drug interaction involved in the ADR?		
6	Was poor compliance involved in the ADR?		
7	Was a toxic serum concentration or a laboratory? monitoring test documented?		

Seriousness analysis was based on the protocols followed by the national center of pharmacovigilance and applied by the center staff, seriousness was assessed according to the ICSR paper (table 4).

Table 4. Seriousness assessment in the Individual Case Safety Report (20)**.**

Do you consider the reaction to be serious? Yes ☐ No ☐	
If yes, please tick (✓) to indicate why the reaction is considered to be serious:	
☐ The patient died due to the reaction	☐ Involved or prolonged inpatient hospitalization
☐ Life threatening	☐ Involved persistent or significant disability or incapacity
☐ Congenital anomaly	☐ medically significant, please give details:

The outcome for each ICSR was recorded and categorized into one of following categories by the WHO: fetal, not recovered/not resolved, recovered / resolved, recovered / recovered with sequelae, recovering /resolving and unknown in case of missing data in this field of the report.

Ethical approval

The study had been approved by the scientific committee of the University of Baghdad/ College of Pharmacy and the Iraqi Ministry of Health/ Department of Research and Development before it was conducted

Statistical analysis

Analysis of data was carried out using Microsoft- excel. Data were presented in simple measures of frequency and percentage.

Results

Age group analysis showed that adults were the major group (87.29%). Regarding gender distribution, the majority of the reports was for females (78.81%). Pharmacists were the most common reporters (74.58%). Regarding the province of reports, it was not available in (22.03%) of the reports and the highest number of reports were from Najaf (18.64%) (table 5).

Table 5. Age group, gender, reporter and province distribution of ICSRs.

Age group	**ICSR number (%)**
Adult	103 (87.29%)
Elderly	10 (8.47%)
N/A	3 (2.54%)
Infant	2 (1.69%)
Gender	**ICSR number (%)**
Female	93 (78.81%)
Male	19 (16.10%)
N/A	6 (5.08%)
Reporter	**ICSR number (%)**
Pharmacist	88 (74.58%)
N/A	23 (19.49%)
Physician	5 (4.24%)
Other Health Professional	2 (1.69%)
Province	**ICSR number (%)**
N/A	26 (22.03%)
Al-Najaf	22 (18.64%)
Nineveh	20 (16.95%)
Baghdad	13 (11.02%)
Karbala	9 (7.63%)
Al-Basra	8 (6.78%)
Al-Anbar	6 (5.08%)
Babylon	6 (5.08%)
Salah Al-din	4 (3.39%)
Kirkuk	3 (2.54%)
Diyala	1 (0.85%)
Characteristics of ICSR	**ICSR number (%)**
Docetaxel as a single Agent	100 (84.7%)
Combination with cyclophosphamide and doxorubicin	7 (5.9%)
Combination with trastuzumab	5 (4.2%)
Combination with cisplatin	4 (3.2%)
Combination with gemcitabine	1 (0.8%)
Combination with 5-flurouracil	1 (0.8%)

N/A: Not Available, **ICSR**: Individual Case Safety Report

According to SOC, the ADRs distribution for docetaxel showed that "skin and subcutaneous tissue disorders" (26.7%), "respiratory, thoracic and mediastinal disorders" (20.8%), "gastrointestinal disorders" (17.4%) and "general disorders and administration site conditions" (10.6%) were the most frequently reported ADRs. Docetaxel adverse drug reactions are listed in (table 6) in the preferred term grouped by SOC.

Table 6. ADRs in preferred term grouped by system organ classification for docetaxel

ADRs		
Skin and subcutaneous tissue disorders	**63**	**(26.7%)**
Pruritus	13	(5.5%)
Dermatitis exfoliative	10	(4.2%)
Nail discoloration	10	(4.2%)
Skin exfoliation	7	(3.0%)
Skin discoloration	6	(2.5%)
Erythema	5	(2.1%)
Skin burning sensation	4	(1.7%)
Skin ulcer	2	(0.8%)
Hyperhidrosis	1	(0.4%)
Rash	1	(0.4%)
Rash generalized	1	(0.4%)
Rash papular	1	(0.4%)
Skin depigmentation	1	(0.4%)
Swelling face	1	(0.4%)
Respiratory, thoracic and mediastinal disorders	**49**	**(20.8%)**
Dyspnea	22	(9.3%)
Interstitial lung disease	13	(5.5%)
Cough	3	(1.3%)
Hyperventilation	3	(1.3%)
Choking	2	(0.8%)
Epistaxis	2	(0.8%)
Respiratory disorder	2	(0.8%)
Choking sensation	1	(0.4%)
Oropharyngeal pain	1	(0.4%)
Gastrointestinal disorders	**41**	**(17.4%)**
Nausea	19	(8.1%)
Vomiting	11	(4.7%)
Diarrhea	4	(1.7%)
Abdominal pain	2	(0.8%)
Abdominal discomfort	1	(0.4%)
Abdominal pain upper	1	(0.4%)
Aphthous ulcer	1	(0.4%)
Epigastric discomfort	1	(0.4%)
Mouth ulceration	1	(0.4%)
General disorders and administration site conditions	**25**	**(10.6%)**
Pyrexia	6	(2.5%)
Swelling	4	(1.7%)
Administration site extravasation	2	(0.8%)
Chest discomfort	2	(0.8%)
Influenza like illness	2	(0.8%)
Administration site rash	1	(0.4%)
Chest pain	1	(0.4%)
Chills	1	(0.4%)

Table 6 continued . ADRs in preferred term grouped by system organ classification for docetaxel

ADRs		
Extravasation	1	(0.4%)
Fatigue	1	(0.4%)
Feeling cold	1	(0.4%)
Injection site pain	1	(0.4%)
Instillation site erythema	1	(0.4%)
Edema peripheral	1	(0.4%)
Immune system disorders	**15**	**(6.4%)**
Hypersensitivity	12	(5.1%)
Drug hypersensitivity	2	(0.8%)
Immune system disorder	1	(0.4%)
Musculoskeletal and connective tissue disorders	**11**	**(4.7%)**
Arthralgia	5	(2.1%)
Myalgia	3	(1.3%)
Back pain	1	(0.4%)
Bone pain	1	(0.4%)
Muscular weakness	1	(0.4%)
Nervous system disorders	**8**	**(3.4%)**
Headache	3	(1.3%)
Hypoesthesia	2	(0.8%)
Burning sensation	1	(0.4%)
Demyelination	1	(0.4%)
Dizziness	1	(0.4%)
Infections and infestations	**6**	**(2.5%)**
Candida infection	1	(0.4%)
Oral candidiasis	1	(0.4%)
Oral fungal infection	1	(0.4%)
Q fever	1	(0.4%)
Skin infection	1	(0.4%)
Wound infection bacterial	1	(0.4%)
Cardiac disorders	**3**	**(1.3%)**
Tachycardia	3	(1.3%)
Metabolism and nutrition disorders	**3**	**(1.3%)**
Decreased appetite	2	(0.8%)
Fluid retention	1	(0.4%)
Blood and lymphatic system disorders	**2**	**(0.8%)**
Anemia	1	(0.4%)
Neutropenia	1	(0.4%)
Eye disorders	**2**	**(0.8%)**
Lacrimation increased	2	(0.8%)
Injury, poisoning and procedural complications	**2**	**(0.8%)**
Burn esophageal	1	(0.4%)
Ligament rupture	1	(0.4%)
Vascular disorders	**2**	**(0.8%)**
Flushing	1	(0.4%)

Table 6 continued. ADRs in preferred term grouped by system organ classification for docetaxel

ADRs		
Hypotension	1	(0.4%)
Ear and labyrinth disorders	**1**	**(0.4%)**
Tinnitus	1	(0.4%)
Investigations	**1**	**(0.4%)**
Respiratory rate decreased	1	(0.4%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1**	**(0.4%)**
Cancer pain	1	(0.4%)
Reproductive system and breast disorders	**1**	**(0.4%)**
Menstruation irregular	1	(0.4%)
Grand Total	**236**	**(100.0%)**

Causality assessment showed that most of the ADRs was in the "possible" category with 68.6% followed by 24.2% for probable, 3.4% for unclassified, 2.5% for unlikely and 1.3% for Certain category. Severity analysis showed that Level 3 was the major category with 55.5% of ADRs falling in this category followed by 19.9% for Level 4, 12.3% for Level 1, 8.1% for Level 2, 3.8% for Level 5 and 0.4% for Level 7. Expectedness analysis showed that 80.5% of the ADRs associated with docetaxel was expected ADRs while 19.5% of the ADRs were unexpected. Preventability analysis showed that 93.2% of the ADRs were in the possibly preventable category, 3.8% were non-preventable and 3% were recorded as preventable. The outcome of the ADRs associated with docetaxel were mainly in the recovered / resolved category with 46.2%, followed by 15.3% (15.25%) in the not recovered / not resolved / ongoing category, 6.4 (6.36) % were in the recovering / resolving category, 0.9 (0.85)% in the recovered / resolved with sequelae category, 0.4 (0.42)% of the ADRs were recorded as fatal and 30.9 (30.93)% of the ADRs were missing the data regarding the outcome of the reaction. The seriousness analysis of the ADRs with docetaxel showed that 80.5% of the ADRs were serious while 14.8% of the ADRs were non-serious, 4.7% of the ADRs were missing some data to assess seriousness.

Table 7. Causality, severity, expectedness, preventability, seriousness and outcome of ADRs reported for Docetaxel

Causality	**Number of ADRs (%)**
Certain	3 (1.3%)
Probable	57 (24.2%)
Possible	162 (68.6%)
Unclassified	8 (3.4%)
Unlikely	6 (2.5%)
Severity	
Level 1	29 (12.3%)
Level 2	19 (8.1%)
Level 3	131 (55.5%)
Level 4	47 (19.9%)
Level 5	9 (3.8%)
Level 7	1 (0.4%)
Expectedness	
Expected	190 (80.5%)
Unexpected	46 (19.5%)
Preventability	
Non-Preventable	9 (3.8%)
Possibly preventable	220 (93.2%)
Preventable	7 (3.0%)
Outcome	
Fatal	1 (0.42%)
Not Recovered / Not Resolved / Ongoing	36 (15.25%)
Recovered / Resolved	109 (46.19%)
Recovered / Resolved with Sequelae	2 (0.85%)
Recovering / Resolving	15 (6.36%)
Unknown	73 (30.93%)
Seriousness	
No	35 (14.8%)
Unknown	11 (4.7%)
Yes	190 (80.5%)

Discussion

The current study showed that most of the ADRs were among the adult age group (87.29%) (Table-5), the gender distribution showed more ADRs in the female patient group than in the male patient group this may be attributed to the greater use of docetaxel in the treatment of breast cancer which lead to the development of more ADRs for this medication in the adult and female gender. The results showed that the reporters of the ADRs were mostly pharmacists which indicate that the pharmacovigilance responsibility in the healthcare facilities are more held by pharmacists. Regarding the province of reporting, Al-Najaf and Nineveh showed the most ICSRs reported across Iraq despite the unstable security situation in Nineveh and this result is consistent with result from another pharmacovigilance study in Iraq that showed that Nineveh was the major contributor to the ICSRs reporting[21], although docetaxel was a single medication in around 85% of cases, the presence of concomitant anti-cancer medications in less than 20% of the total cases affected the level of final certainty.

The most commonly observed ADRs in the current study were in the "skin and subcutaneous tissue disorders" (26.7%), followed by "respiratory, thoracic and mediastinal disorders" (20.8%), "gastrointestinal disorders" (17.4%) and "general disorders and administration site conditions" (10.6%) (Table 6) and the most common ADRs were nausea, vomiting, dyspnea, skin disorders, nail discoloration and hypersensitivity respectively which is consistent with the most commonly occurring ADRs according the summary of product characteristics by the EMA but the hematological ADRs like neutropenia and anemia were under observed in the study with (0.4%) for each (Table 6) compared to the summary of product characteristics [12], According to a report published by the Iraqi Pharmacovigilance Center there was an increase in cutaneous and respiratory adverse reactions of docetaxel few years ago that required a regulatory action at that time [22].

Adverse drug reactions causality assessment showed that most of the ADRs were in the possible category followed by probable and very few in certain category that's because for an ADR to be considered as certain, many criteria must be met (time sequence, disease or other drug causality ruled out, dechallenge and rechallenge)[23] and these criteria specially the rechallenge is rarely experienced with ADRs occurring after an anticancer medication, rechallenge may not be needed for a certain classification in a small number of situations such as when a cytotoxic drug extravasates and causes tissue damage which is the case with the 3 certain ADRs reported in the study, but for probable category rechallenge is not required so more ADRs fall in this category. For possible category, the ADR is suspected to be caused by other drugs or can be caused by the disease condition being treated.

For severity assessment of ADRs, Level 3 severity accounts for (55.5%) of the ADRs as shown in (Table 7) indicating that the majority of the ADRs required antidote or other medication for the ADRs with no increase in hospitalization time which takes place in the Level 4 category which represent 19.9% of the ADRs. Both Level 3and 4 constitute the moderate category of the severity assessment[17]. There was one ADR that result in death of the patient and the reaction was (bacterial infectious disorders) with possible causality. The preventability analysis showed that most of the ADRs were possibly preventable due to missing data that lead to the conclusion weather it was definitely preventable or non-preventable. The outcome for docetaxel ADRs was mostly recovered / resolved ADRs with (46.19%) while data regarding ADRs outcome were missing in (30.93%) (Table 7). A study for the presentation and management of docetaxel related ADRs was conducted in Canada stated that most of the common treatment related toxicities are resolved either between cycles of the drug or by treatment discontinuation[11]. Seriousness analysis showed that 80.5% of ADRs were serious which may reflect the idea that non-serious ADRs were underestimated by the health care providers and was not reported accordingly and the focus was directed on reporting serious ADRs to the National Pharmacovigilance Center.

The current study is not without limitations. The main limitation was the incompleteness of the reports reported by the health facilities to the pharmacovigilance center as the reporter is mainly focusing on the ADRs but less focus on the patient medical history, concomitant medications and patient follow up and these data are necessary to establish the causality, preventability and other parameters more accurately.

Conclusions and recommendations

Docetaxel has a wide range of side effects profile affecting mainly the skin, respiratory and gastrointestinal systems with most of these side effects being expected, serious and moderately severe. More focus should be directed towards side effects for proper management and prevention also there should be a continuous awareness regarding the importance of pharmacovigilance in all health care facilities and the employees responsible in these facilities should be professionally trained so that the reported data be accurate and can be analyzed properly for better health outcome. Also patients should be educated about the possible side effects for their medications and how to report in case these side effects occur.

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