Docetaxel: Regulatory action in Iraq based on new safety information

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ABSTRACT

Docetaxel is a member of the Taxane's family used in cancer chemotherapy. During 2014, Iraqi pharmacovigilance centre (IPC) started to receive reports regarding increased adverse events (AEs) accompanying Docetaxel treatment and at the end of the same year, the number of reports reached 30 reports compared to 8 reports during 2012 and 2013. Reports came from many oncology centres in Iraq. Particularly 2 types of AEs were reported, about 56.7% of the reported cases demonstrated skin and subcutaneous tissue disorders, first of which being dermatitis exfoliative, along with gloves and stockings pattern of black pigmentation of skin and subcutaneous tissue and about 33.3% of the reported cases were interstitial lung disease (interstitial pneumonitis), patients also experienced episodes of severe dyspnoea and orthopnoea (Breathlessness on lying flat) hours after receiving the dose. More than 100 cases went unreported. Many regulatory actions were taken and the final decision was canceling the primary registration of specifically branded Docetaxel.

Key words: Docetaxel, skin, respiratory, pharmacovigilance.

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INTRODUCTION

Docetaxel is an important antimicrotubule agent of the Taxane's family. It is a semisynthetic derivative of paclitaxel but more potent than the later, derived from extracts of the leaves of the European yew tree (Taxus baccata), was discovered in the 1980s.[1]

Docetaxel inhibits mitosis resulting in cell death.[2] It is commonly used in the treatment of a variety of solid tumours; breast, prostate, lung, head and neck tumours. It is given for adults as Intravenous infusion, either as monotherapy in a dose of 100 mg/m² or in combination with other agents in a dose of 60 to 100 mg/m².[3]

Like other antineoplastic agents, it has a very high ADRs profile. Neutropenia and leukopenia, are the major ADRs and because of serious hypersensitivity reactions including dyspnea, urticaria, and hypotension, premedication with dexamethasone and diphenhydramine and an H2 blocker is required in patients who are treated with docetaxel.[4]

Literature and labelling; The preparation used in Iraq was under national drug code (NDC Code 45963-734-54). It is used as a single-dose vials. Each millilitre contains: 20 mg docetaxel, 6 mg citric acid anhydrous, 100 mg povidone p12, 424 mg polysorbate 80, 400 mg ethanol as single-dose vials ready for intravenous infusion.[5]

The skin and subcutaneous side effects stated in the company's summary of product characteristics (SmPC) are reversible cutaneous reactions that are generally considered as mild to moderate and they rarely lead to interruption or discontinuation of docetaxel. Severe symptoms such as eruptions followed by desquamation are less frequently reported and rarely lead to interruption or discontinuation of docetaxel treatment.[6]

Literature review revealed that skin and hair reaction is more commonly associated with docetaxel including palmar/plantar erythrodysaesthesias (hand foot syndrome), scattered macular/papular rash, vein tracking (with peripheral administration), nail ridging and onycholysis.[7]

Other expected side effects of Docetaxel

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individually are alopecia, bone-marrow suppression, cystoid macular oedema, extravasation, fatal respiratory disorders, gastro-intestinal toxicity, heart failure, hypersensitivity reactions, hyperuricaemia, nausea, oral mucositis, peripheral neurotoxicity, persistent fluid retention (commonly as leg oedema that worsens during treatment) which can be resistant to treatment, severe skin reactions, thromboembolism, tumour lysis syndrome and vomiting.[8]

Reports in the Iraqi database: At the end of 2014, 30 individual case safety reports (ICSRs) piled in Iraqi DATABASE of adverse drug reactions. Particularly, two types of adverse events; skin and subcutaneous tissues and Respiratory and thoracic disorders. All were reported by pharmacists, and labelled as serious according to CIOMS criteria.[9] No concomitant medications were reported and docetaxel was the only suspected drug.

As shown in table 1, Skin and subcutaneous tissue disorders shows more than 50% of reported adverse events (AEs), while Respiratory, thoracic and mediastinal disorders represents more than 30% of reported AEs.

Patient's demography: Females were being affected in 77.4 % of reported cases, and the age group between 46-64 years was the mostly affected. Table 2

Skin manifestations: According to the notes of the treating physicians, the pigmentation site being specifically, painless showing mottled skin, and including the nails, appearing 7 days after the dose. Some of these patients have the pigmentation becoming less dark with the administration of the subsequent doses. The burn like skin reactions disappear weeks after discontinuation of the medicine. As shown in table 3, dermatitis exfoliative and nail discolouration were the most reported preferred terms (PT).

Respiratory manifestations: According to the notes of the treating physicians, respiratory symptoms were not treated according to a specific expected pathophysiology and never seemed to be relieved even weeks after stopping the medication. Patients had been referred to medical and emergency treatment of the symptoms, and it is worth mentioning that some were treated by advanced airways management (including endotracheal intubation). Cases of hyperventilation and epistaxis unrelated to a prior bleeding disorder have been reported. Some patients experienced episodes of severe dyspnoea and orthopnoea (Breathless-

Table 1: Reported adverse events of docetaxel in Iraq during 2014.

Reaction	Count	%
Soc: cardiac disorders	1	3.3
Soc: ear and labyrinth disorders	1	3.3
Soc: gastrointestinal disorders	6	20.0
Soc: general disorders and administration site conditions	3	10.0
Soc: immune system disorders	6	20.0
Soc: infections and infestations	2	6.7
Soc: metabolism and nutrition disorders	1	3.3
Soc: musculoskeletal and connective tissue disorders	5	16.7
Soc: nervous system disorders	2	6.7
Soc: respiratory thoracic and mediastinal disorders	10	33.3
Soc: skin and subcutaneous tissue disorders	17	56.7

(soc: system organ classification)

Table 2: Age groups of patients who were reported to have adverse events from using docetaxel during 2014.

Age groups	Count	%
18 - 44 years	8	26.7
45 - 64 years	16	53.3
65 - 74 years	4	13.3
≥ 75 years	2	6.7

Table 3: Skin and subcutaneous tissue disorders reported from using docetaxel during 2014.

Reaction	Count	Percentage
PT: Dermatitis exfoliative	7	41.2
PT: Nail discolouration	6	35.3
PT: Pruritus	5	29.4
PT: Skin exfoliation	5	29.4
PT: Skin burning sensation	2	11.8
PT: Skin discolouration	2	11.8
PT: Skin depigmentation	1	5.9

Table 4: Respiratory, thoracic and mediastinal disorders reported from using docetaxel during 2014

Reaction	Count	Percentage
PT: Dyspnoea	8	72.7
PT: Hyperventilation	2	18.2
PT: cough	1	9.1
PT: Epistaxis	1	9.1

ness on lying flat) hours after receiving the dose as shown in **table 4**.

Outcome: Many Patients have been improved after stopping (dechallenge) the medicine and some patients suffered the same adverse events after re- introducing (rechallenge) the medicine. The outcome of 9 AEs were unknown, 28 AEs were not recovered at the time of reporting, and 34 AEs were reported recovered.

DISCUSSION

In this report, docetaxel was given as a monotherapy in all reported cases. The cases were reported from many oncology centres in Iraq; they were clustered in the oncology centres at Medical City in Baghdad, Duhok, Basrah, Najaf, and Ninavah. In addition, few cases were scattered in areas where this culprit drug had been used. Other oncology centres which were using docetaxel of other branded at that time have not reported such AEs.

All the skin AEs reported to our centre after the used of docetaxel were serious necessitating discontinuation of the drug. However, the SmPC of the company has stated that most of the skin AEs are mild to moderate, and sometimes severe but it rarely leads to discontinuation of the treatment.

During the same period, the WHO global database of individual case safety reports (ICSRs), VigiBase, has reported that skin and subcutaneous tissue disorders, and respiratory, thoracic and mediastinal disorders were about 20% and 10% respectively.[10] These figure are relatively much lower than ours which were 56.7% for skin and subcutaneous tissue disorders and 33.3% for respiratory, thoracic and mediastinal disorders.

Before 2013, only one brand of docetaxel was registered and used in Iraq. However, for the sake of competition and due to budget limitation, another brand of docetaxel (the culprit) was distributed among Iraqi health institutions in 2014. All the available tests in the National Centre for Drug Control and Research (NCDRC) were performed and they were complied before releasing the batches for use.[11] The drug was registered primarily according to the valid regulations at that time. KIMADIA; the body responsible for procurement and distribution of medicines and health appliances at Ministry of Health in Iraq, has procured and distribute this brand to meet the need of oncology centres in Iraq.

The progressive emergence of these adverse events has led to a decisive decision of stop using the drug in Iraq. And over the following three years use of docetaxel has been subjected to so many assessments, evaluations, and investigations by many administrative, scientific and inspective committees. The final decision was to cancel the registration of the culprit brand of docetaxel. The justification of this decision was due to increased occurrence of the adverse events of this brand, the stability problems (stability study of the drugs was performed by the company in zone 3 countries while Iraq is one of zone 4 countries), and high ethanol content. The company was involved and informed with all these events and actions and was pursued legally by Ministry of Health. It is worth mentioning that during 2014, the issue of high ethanol content in different docetaxel preparations was raised by the US Food and Drug Administration (FDA). The FDA warned of alcohol intoxication, especially in high risk patients or when using it with other medications.[12]

CONCLUSIONS

Iraqi drug regulatory authority, like its counterparts in the world is responsible for delivering safe and effective drugs. Any new safety concerns will initiate a process of evidence-based decision making. Accordingly, the new safety information regarding increased skin and respiratory AEs occurred due to use of docetaxel was made available through the Iraqi spontaneous reporting system of adverse drug reaction, and the final decision was suspension of the specifically branded docetaxel in Iraq due to major safety concerns.

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Abbreviation list: Adverse events (**AEs**), Adverse Drug Reactions (**ADRs**), Individual case safety reports (**ICSRs**), Preferred terms (**PT**), Summary of product characteristics (**SmPC**), System organ classification (**SOC**)

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