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Case Report

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Fatal Medullar Aplasia: Is DOCETAXEL Responsible? About Six Cases

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Abstract

Docetaxel is a frequently used chemotherapeutic agent in the treatment of solid cancers. The medical oncology service of UHE-Oran has notified serious adverse reactions such as: Medullary Aplasia (M.A) and toxic shock linked to the use of Docetaxel, this study is about six patients with five fatal evolutions. The Pharmacovigilance team led an investigation in order to analyze the cases and estimate the imputability. Pharmacological studies revealed that Docetaxel is metabolized by the CYP3A4 isoenzyme, so its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. To improve the safety profile of Docetaxel usage another prospective study will start in October 2017

Keywords: CYP 3A4 inhibitors; Docetaxel; Imputability estimation; Medullar aplasia; Taxane toxicity

Introduction

Docetaxel is an antineoplastic agent belongs to the taxoid family [1], frequently used to treat different kinds of cancer, including cancers of the breast, prostate, stomach, head and neck cancers, and non-small-cell lung cancer [2]. Most common adverse reactions across all Docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia [3].

Patient and Methods

As a response to many statements from the medical oncology service of UHE-Oran; concerning the appearance of serious side effects linked to the use of Docetaxel such as: Medullary Aplasia (M.A), toxic shock and death, we carried out a Pharmacovigilance investigation. The statements were about six patients using Docetaxel, with five fatal evolutions; their information is illustrated in the following table (Table 1)

Patient	Age	Cancer	Protocol	Cure	Last cure Date	Evolution
H.N	44	breast	TH	C2	43075	Death
M.F	41	breast	AT	C1	30/05/2017	Death
S.N	26	breast	AT	C3	42802	Death
B.F	41	breast	AT	C4	42893	Death
C.K	70	Cavum	PTX	C2	42894	Death
F.M	35	Cavum	PTX	C2	16/08/2017	M.A
TH: Taxotère® - Herceptine®;AT: Adriamycine® -Taxotère® ;PTX :Cisplatine® -Taxotère®- Xeloda®						

Table 1: Six Patients Using Docetaxel, With Five Fatal Evolutions; Their Information.

Results

The results of imputability estimation according to the updated French method are resumed in (Table 2).

Patient	Protocol	Intrinsec Imputability	Extrinsec Imputability
H.N	Docetaxel	C2S3→ I5	B4
	TAXOTERE®		
	Sanofi laboratoiry		
	Batch N°6F278A		
	Trastuzumab	C2S2 →I3	B4
M.B.F	Docetaxel	C2S2→ I3	B4
	TAXOTERE®		
	Sanofi laboratoiry		
	Batch N°6F278A		
	Doxorubicine	C2S2 → I3	B4
S.N	Docetaxel	C2S1 → I2	B4
	DOCETAX®		
	Cipla laboratoiry		
	Batch N°GE60636		
	Doxorubicine	C2S1→ I2	B4
B.F	Docetaxel	C2S2 → I3	B4
	TAXOTERE®		
	Sanofi laboratoiry		
	Batch N°6F295A		
	Doxorubicine	C2S2→ I3	B4
C.K	Docetaxel	C2S3→ I5	B4
	DOCETAX®		
	Cipla laboratoiry		
	Batch N°GE60636		
	Capecitabine	C2S2→ I3	B4
	Cisplatine	C2S2 → I3	B4
F.M	Docetaxel	C2S2→ I3	B4
	DOCETAX®		
	Cipla laboratoiry		
	Batch N°GE60636		
	Capecitabine	C2S2→ I3	B4
	Cisplatine	C2S2 → I3	B4
Intrinsec imputability Illustration , Extrinsec imputability Illustration: B4 :Labeled side effect			

Table 2: Imputability Estimation According to the updated French method.

Discussion

Drug interactions

Docetaxel is metabolized by the CYP 3A4 isoenzyme. About 80 % Docetaxel is eliminated in faeces during the first 48 hours as inactive metabolites. An association between docetaxeland a powerful inhibitor of 3A4 cytochrome will reduce Docetaxel metabolism, which will lead to an elevation of its blood concentration and thus increasing its toxicity [4]. The main inhibitors of the CYP3A4 are:

- Grapefruit Juice
- Amiodaron
- Calcic Channels Antagonistic (Diltiazem, Verapamil),
- Antifungal Drugs (Ketoconazol, Itraconazol, Fluconazol, Miconazol, Posaconazol, Voriconazole),
- Delavirdin,
- Proteases Inhibitors (Ritonavir, Nelfinavir, Amprénavir, Indinavir, Atazanavir),
- Imatinib,
- Macrolide (Erythromycin, Clarithromycin, Josamycin, Telithromycin),
- Association Quinupristin + Dalfopristin,
- Stiripentol.

On the other hand, the incidence of the febrile neutropenia accompanied or not with sepsis is higher in patients treated with Trastuzumab and Docetaxel than it is with Docetaxel [5].

ANSM investigation

On March 2017, a signal of colitis and septic shocks has been confirmed with Docetaxel (originator and generics). To improve knowledge of the safety profile of Docetaxel, another study has been performed on all the adverse drug reactions. Moreover, a same study has been performed for paclitaxel, alternative to Docetaxel in the treatment of breast cancer [6]. Adverse drug reactions reported between 1995 and 03/04/2017 were:

- Skin disorders (26%)
- General disorders: malaises, asthenia, fever, pain, oedema, mucositis (12%)
- Gastro-intestinal disorders (11%)
- Blood disorders (10%)
- Respiratory disorders (7%)
- Musculoskeletal disorders (6%)
- Nervous system disorders (5%)
- Infections (4%)
- Vascular disorders (3%)
- Immune system disorders (3%)
- Cardiac disorders (2%)

These results show that increase of “Serious” or “Fatal” adverse drug reactions since 2010: concerns all taxanes and not only Docetaxel mainly concerns dose dependant toxicities, suggesting a problem of concentration Occurrence or complications for some adverse drug reactions could be limited by a simple surveillance (blood numeration, gastrointestinal symptoms, and hepatic surveillance), dose adaptation for the next treatment and a systematic use of G-CSF that is currently recommended only if there are risk factors [6].

Conclusion and Perspectives

The Pharmacovigilance team plans to lead a prospective study in order to survey and prevent serious side effects. This study will start in October 2017. Monitoring Docetaxel plasmatic level by chromatographic method will be the main aim of our team, to optimize the treatment’s quality.

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