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A STUDY ON THE ASSESSMENT OF FACTORS INFLUENCING VARIOUS ADVERSE DRUG REACTIONS OF DOCETAXEL IN CARCINOMA BREAST PATIENTS IN TERTIARY CARE HOSPITALS OF KOLKATA.

Pharmacology

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ABSTRACT

Backgound - Docetaxel is a very commonly used cancer chemotherapeutic drug having limitations of its various Adverse Drug Reactions (ADRs). Therefore assessment of risk benefit ratio is essential before treating any patient with Docetaxel.
Objective-To identify factors influencing various ADRs of Docetaxel.
Methodology-A prospective study conducted on 52 breast cancer patients getting Docetaxel in Radiotherapy department of R.G.Kar Medical College & Hospital and IPGMER & SSKM Hospital, Kolkata were assessed for development of any Adverse Drug Reaction. Study variables were - age, body mass index, performance status, hemoglobin level, co-morbidities like hypertension and diabetes. In this study it was seen whether any association were found between study variables and ADRs.
Result- Most of the Adverse Drug Reactions was associated with older age group and poor performance status and low hemoglobin level. Association was found between hypertension with fluid retention syndrome; diabetes with myelosupression, peripheral neuropathy and fatigue.
Conclusion-Various Adverse Drug Reactions of Docetaxel were associated with various patient related factors.

KEYWORDS

Docetaxel, Adverse Drug Reaction, Risk benefit ratio.

INTRODUCTON:

Docetaxel is a semisynthetic Taxane with proven efficacy in a variety of solid tumors, including breast cancer. It's mechanism of action is to stabilize microtubules by preventing their depolymerisation, thus disrupting normal cell division (1). Taxanes are often the treatment of choice either as single agents or in combination in patients who are at risk for cardiac complications due to prior Anthracycline exposure and those who developed metas¬tases less than 12 months after prior Anthracycline-based adjuvant therapy. Chemotherapy kills cells at a faster rate than the re-growth of the cells. All chemotherapeutic agents known to date are toxic for the tumors as well as the host cells. The limitation of chemotherapy is their Adverse Drug Reactions. Therefore evaluation of risk benefit ratio is most important before starting chemotherapy. For risk benefit ratio assessments of the factors influencing different Adverse Drug Reactions are required.

METHODOLOGY:

Study subjects: 52 patients receiving Docetaxel monotherapy in carcinoma breast patient.

Study design: Longitudinal prospective study.

Study setting: R.G.Kar Medical College & Hospital and I.P.G.M.E.R. & S.S.K.M. Hospital, Kolkata.

Ethical considerations: The Hospital ethical committee approval was obtained to carry out the study. Informed consent was obtained from each patient.

Inclusion criteria:

1. All histologically proved invasive ductal carcinoma of Breast patient receiving single agent Docetaxel.
2. Already undergone surgery for breast carcinoma.
3. Patient completed three to four cycles of FEC (5FU, Epirubicin, Cyclophosphaide)/AC (Adriamycin, Cyclophosphamide).

Exclusion criteria:

1. Pregnant & lactating mother.
2. Carcinoma breast along with other malignancy.
3. Breast carcinoma patient who have got radiotherapy previously.
4. Breast cancer patients who have got chemotherapy or radiotherapy previously for another malignancy.
5. Breast cancer Patients receiving Docetaxel as combination chemotherapy.
6. Patients with performance status ECOG-3-4.

Study variables:

1. Age-Grouped into 30-49 years, 50-64 years, ≥65 years.
2. BMI-Grouped into BMI up to 17.99, 18-24 and ≥25
3. Performance status-According to ECOG scoring system, Grouped into ECOG-0, ECOG-1, ECOG-2
4. Hemoglobin Level-Grouped into <10 gm/dl and ≥10 gm/dl
5. Co morbidities –Hypertension on medication-yes or no, Diabetes Mellitus on medication-yes or no.

Study protocol: In this study all carcinoma breast patients receiving 3-4 cycles of FEC (5FU-500 mg/m2 i.v., Epirubicin-100mg/m2 i.v., Cyclophosphamide-100mg/m2)/AC (Doxorubicin-60 mg/m2 i.v, Cyclophosphamide - 600mg/m2 i.v.) followed by 3-4 cycles of Docetaxel monotherapy every 21 days as per chemotherapy protocol were selected. In the OPD patients were clinically assessed. Following blood reports were checked - complete hemogram, LFT, Alkaline phosphatase, SGOT and SGPT, serum urea, creatinine, FBS and PPBS. ECG, Echocardiography and chest X-ray reports were also checked. Those patients with Hb% level <10 gm/dl were given blood transfusion to reach the Hb% level ≥ 10 gm/dl prior to Docetaxel administration. Every patient was given prior premedication with steroid & GCSF prophylaxis. Patients were assessed on the day of Docetaxel (80-100mg/m2) monotherapy infusion and they were reassessed during their subsequent visits for development of ADRs & if any was graded according to ECOG (Eastern Cooperative Oncology Group) criteria. Clinical parameters were assessed during next review visit & the biochemical parameters were evaluated as prescribed by the physician.

Each patient was examined during 3 cycles of Injection Docetaxel. ADRs were assessed on the basis of their age, BMI, performance status, hemoglobin level and the co morbidities like hypertension and diabetes mellitus separately.

STATISTICAL ANALYSIS: Chi-square test, Fisher's Exact test were performed to see association between study variables and ADRs. P value <0.05 were considered significant.

RESULTS: In this study total 52 patients who fulfilled inclusion & exclusion criteria were included. Out of these 53.8% patients were in the age group 30-49.99 years, 34.7% were in the age group 50-64.99 years, 11.5% patient were >65 years. Mean age being 48.9. Out of the 52 patient 9.6% patient's BMI were up to 17.99, maximum patient's (46.2%) BMI>25. Mean BMI was 24.154. Most of the patient's (78.8%) Hb level was ≥10 (gm/dl). Maximum patient's (65.4%) performance status was ECOG-1, 11.5% patients had ECOG-0 and

23.1% patients ECOG-2. Patients with hypertension on medication were 26.9%. Pre-existing diabetes on medication were 21.2%.

Table-1

Association between Patient Characteristics and Adverse drug reactions of DOCETAXEL among breast cancer patients (N=52)

Character	Number	Myelosuppression NO(%)	Hypersesitivty reaction NO(%)	Fluid retention syndrome NO(%)	Diarrhoea NO(%)
Age	28	4(14.3)	4(14.3)		18(64.3)
30-49	18	4(22.2)	3(16.7)	6(21.4)	13(72.2)
50-64	06	5(83.3)	00(0)	9(50.0)	0(0)
≥65		***0.002***	*0.740*	4(66.7)	***0.005***
Significance (p value)				***0.038***	
BMI	05	3(60)	4(80)	2(40)	5(100)
Upto17.99	23	2(8.7)	1(4.3)	5(21.7)	15(65.2)
18-24.99	24	8(33.3)	2(8.3)	12(50)	11(45.8)
≥25		*0.020*	***0.001***	*0.147*	*0.058*
Significance (p value)					
Hb level	11	7(63.3)	3(27.3)	6(54.5)	7(63.6)
<10(gm/dl)	41	6(14.6)	4(9.8)	13(31.7)	24(58.5)
≥10(gm/dl)		***0.002***	*0.154*	*0.148*	*0.521*
Significance (p value)					
Performance status	06	0(0)	0(0)	2(33.3)	5(83.3)
ECOG-0	34	4(11.8)	1(2.9)	11(32.4)	16(47.1)
ECOG-1	12	9(75.0)	6(50.0)	6(50.0)	10(83.3)
ECOG-2		***0.000***	***0.001***	*0.468*	***0.039***
Significance (p value)					
Pre-existing hypertension (on medication)	38	9(23.7)	7(18.4)	5(13.2)	25(65.8)
No	14	4(28.6)	0(0)	14(100)	6(42.9)
Yes		*0.488*	*0.094*	***0.000***	*0.120*
Significance (p value)					
Pre-existing Diabetes (on medication)	41	7(17.1)	4(9.8)	14(34.1)	26(36.4)
No	11	6(54.5)	3(27.3)	5(45.5)	5(45.5)
Yes		***0.019***	*0.154*	*0.360*	*0.231*
Significance (p value)					

From table 1, associations were found between myelosupression with higher age, low Hb level, poor performance status and diabetes; hypersensitvity reaction with low BMI and poor performance status; fluid retention syndrome with age and hypertension; diarrhoea with age and performance status.

Table -2 Association between Patient Characteristics and Adverse Drug Reactions of DOCETAXEL among breast cancer patients (N=52)

Character	Number	Nausea & vomiting NO(%)	Mucositis NO(%)	Peripheral neuropathy NO(%)	Fatigue & Asthenia NO(%)
Age	28	23(82.1)	16(57.1)	2(7.1)	5(17.9)
30-49	18	13(72.2)	14(77.8)	6(33.3)	8(44.4)
50-64	06	6(100)	2(33.3)	6(100)	6(100)
≥65		*0.310*	*0.135*	***0.000***	***0.000***
Significance (p value)					
BMI	05	4(80)	5(100)	0(0)	3(60)
Upto17.99	23	18(78.3)	15(65.2)	4(17.4)	5(21.7)
18-24.99	24	20(83.3)	12(50)	10(41.7)	11(45.8)
≥25		*0.881*	*0.105*	*0.061*	*0.100*
Significance (p value)					
Hb level	11	11(100)	7(63.6)	2(18.2)	8(72.7)
<10(gm/dl)	41	31(75.6)	25(61.0)	12(29.3)	11(26.8)
≥10(gm/dl)		*0.071*	*0.580*	*0.375*	***0.008***
Significance (p value)					
Performance status	06	3(50.0)	3(50)	2(33.3)	2(33.3)
ECOG-0	34	27(79.4)	18(52.9)	8(23.5)	7(20.6)
ECOG-1	12	12(100)	11(91.7)	4(33.3)	10(83.3)
ECOG-2		***0.031***	***0.039***	*0.716*	**0.001**
Significance (p value)					
Pre-existing hypertension (on medication)	38	32(84.2)	24(63.2)	10(26.3)	14(36.8)
No	14	10(71.4)	8(57.1)	4(28.6)	5(35.7)
Yes		*0.254*	*0.466*	*0.565*	*0.603*
Significance (p value)					
Pre-existing Diabetes (on medication)	41	32(78.0)	28(68.3)	5(12.2)	10(24.4)
No	11	10(90.0)	*40.058* (36.4)	9(81.8)	9(81.8)
Yes		*0.314*		***0.000***	***0.001***
Significance (p value)					

From table 2 associations were found between nausea, vomiting and mucositis with performance status; peripheral neuropathy with age and diabetes; fatigue & asthenia with age BMI, performance status and diabetes.

Table -3 Association between Patient Characteristics and Adverse drug reactions of DOCETAXEL among breast cancer patients (N=52)

Character	No	Elevated serum transaminase No(%)	Elevated serum alkaline phosphatase No(%)	Elevated serum bilirubin No(%)
Age				
30-49	28	1(3.6)	4(14.3)	5(17.9)
50-64	18	1(5.6)	4(22.2)	1(5.6)
≥65	06	3(5.8)	0(0)	1(16.7)
Significance (p value)		*0.350*	*0.560*	*0.502*
BMI				
Upto17.99	05	0(0)	2(40.0)	3(60.0)
18-24.99	23	1(4.3)	2(8.7)	3(13.0)
≥25	24	2(8.3)	4(16.7)	1(4.2)
Significance (p value)		*1.000*	*0.177*	***0.005***
Hb level				
<10(gm/dl)		1(9.1)	5(45.5)	4(36.4)
≥10(gm/dl)	11	2(4.9)	3(7.3)	3(7.3)
Significance (p value)	41	*0.518*	***0.007***	***0.029***
Performance status				
ECOG-0	06	0(0)	0(0)	0(0)
ECOG-1	34	0(0)	1(2.9)	0(0)
ECOG-2	12	3(25.0)	7(58.3)	7(58.3)
Significance (p value)		***0.019***	***0.000***	***0.000***
Pre-existing hypertension (on medication)				
No	38	2(5.3)	7(18.4)	5(13.2)
Yes	14	1(7.1)	1(7.1)	2(14.3)
Significance (p value)		*0.618*	*0.300*	*0.617*
Pre-existing Diabetes (on medication)				
No	41	2(4.9)	5(12.2)	4(9.8)
Yes	11	1(9.1)	3(27.3)	3(27.3)
Significance (p value)		*0.518*	*0.216*	*0.154*

From table 3 associations were found between elevated serum transaminase with performance status; elevated serum alkaline phosphatase with Hb level and performance status; elevated serum bilirubin with BMI, Hb level and performance status.

Discussion:

In this study it was seen that older age (≥65yrs) was associated with myelosuppression, fluid retention syndrome, diarrhoea, peripheral neuropathy, fatigue and asthenia. The association between the increasing age (≥65yrs) with myelosuppression corroborate with the study[2] where elderly patients were more sensitive to Docetaxel induced neutropenia. Fatigue and peripheral neuopathy are more common in elderly people, this may be the cause of association. In this study Low BMI was associated with hypersensitivity reaction and elevated bilirubin level. This information could not be compared as relevant literatures are not readily available. Cause of this association may be by chance. Low Hb level was associated with myelosup pression, generalised fatigue and asthenia, elevated serum alkaline phosphatase and elevated serum bilirubin level. Low Hb level may causes further anaemia and low Hb level is one of the cause of fatigue and asthenia. This may be the probable cause of association between low Hb level with myelosuppression and generalised fatigue and asthenia. Here it was found that poorer the performance status more was the Docetaxel related toxicity. This is comparable with the study[3,4]. Another association was found with preexisting hypertension and fluid retention syndrome. However no relevant literature is available to compare this. But hypertension itself causes fluid retention. Preexisting diabetes was associated with myelosuppression, peripheral neuropathy and generalised fatigue and asthenia. In a study [5] statistically significant association was observed for early peripheral neuropathy induced by Docetaxel and pre-existing neuropathy. In another study[6] Diabetes is independent predictors of the development of Taxen-induced peripheral neuropathy. Diabetes itself may cause peripheral neuropathy. Diabetes also causes fatigue and asthenia by i) making the blood sludgy which leads to slowing of circulation ii) through inflammation. So both the factors diabetes and Docetaxel are responsible for the occurrence of peripheral neuropathy and fatigue and asthenia in patients receiving Docetaxel chemotherapy.

CONCLUSIONS:

This study shows that older age, higher performance status, low hemoglobin level, hypertension and diabetes are significantly associated with various Docetaxel induced Adverse Drug Reactions. Hence these are risk factors for Docetaxel induced Adverse Drug Reactions.

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