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A comparative study of Docetaxel versus Paclitaxel in terms of toxicities: A regional cancer centre study in breast cancer

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Abstract: BACKGROUND: In breast cancer patients, docetaxel and paclitaxel likely to have different toxicity profile. Although both have better result in different dosing schedule.

AIMS: A retrospective study compares between two taxenes Docetaxel versus Paclitaxelin terms of their toxicities in breast cancer patients of different BMI (Body Mass Index) and age.

MATERIALS AND METHODS: From January 2014 to August 2015, in two group severity of toxicities as well as the dose reduction, dose delay, granulocyte colony stimulating factor (G-CSF) in 80(40 in AC-D and 40 in AC-P group) patients with operable lymph node-positive (tumor stage T1, T2, or T3 and nodal stage N1 or N2) and high risk, node-negative (T2 or T3, N0) breast cancer without a distant metastases who received adjuvant chemotherapy – 4 cycles adriamycin, cyclophosphamide 3 weekly, followed by 4 cycles docetaxel 3 weekly (AC-D) and 4 cycles adriamycin, cyclophosphamide 3 weekly, followed by 4 cycles paclitaxel 3 weekly (AC-P)- were studied.

RESULTS: The patients in the AC-P group suffered from peripheral neuropathy frequency (P=.025), than those in the AC-D group. Febrile neutropenia was significant in AC-D group (P=.003). A decreasing body mass index was associated with an increased risk of febrile neutropenia (P=.008) and Increasing age was associated with an increased risk of anaemia (P=.003), fatigue (P=.008) and pain (P=.004). Dose reduction and delay occurred due to febrile neutropenia and an increase in aspartate aminotransferase (AST)/alanine aminotransferase (ALT) were more in AC-D group during Docetaxel infusion. So dose reduction was only significant in the AC-D group(P=.001) .

CONCLUSION: In our regional cancer centre, most of the patients are malnourished and from poor socioeconomic status, they poorly tolerates 3 weekly docetaxel leads to dose reduction and delay of next cycle chemotherapy as compared to 3 weekly paclitaxel. Also not follow the weekly paclitaxel. So AC-P preferred over AC-D.

Introduciton:

Among the antineoplastic agents used in breast cancer ,taxanes are in the list of most active drugs. Hopeful result of taxanes chemotherapy in breast cancer these are used as adjuvant setting. Before the 1990s, anthracyclines were the most active agents used as adjuvant as well as metastatic settings. Combination of both taxane –anthracycline has significantly improved the progression free survival(PFS) and response rates in locally advanced breast canceras compared to anthracycline used alone. [1],[2],[3] This anthracyclines-taxanes combinations has given similar results in metastatic breast cancer also. [4],[5] Both taxane (DOCETAXEL& PACLITAXEL) have some common toxicities and also have different toxicity spectrum . Abnormal LFT (Liver function test), neutropenic fever and fluid retention mainly with docetaxel , peripheral neuropathy and pain with paclitaxel . The main purpose of our study to compare toxicities, delay for next cycle , dose reduction and use of GCSF between two taxanes (docetaxel and paclitaxel breast cancer.[6]

Materials and Methods:

From January 2014 to august 2015 total 80 patients of ca breast(LABC) were analysed reterospectively .Tumor stage was T1,T2 or T3 and nodal stage was N1 or N2 but no distant metastasis ,high risk ,node negative without distant metastasis patients were also included all these patients received adjuvant chemotherapy. Fourty patients were in AC-P group and fourty patients were in AC-D group. Four cycles adriamycin, cyclophosphamide (50/500) 3 weekly, followed by 4 cycles docetaxel (75mg/ m2) 3weekly in (AC-D) group, and 4 cycles adriamycin, cyclophosphamide (50/500) 3 weekly, followed by 4 cycles paclitaxel 3 weekly in (AC-P) group were studied . Paclitaxel or docetaxel were administered in patients on the basis of age, performance score and body mass index(BMI) etc. In both groups after receiving first cycle chemotherapy, complete blood count picture , biochemical profile ,physical examination were evaluated properly before next cycle .Accordingly need for GCSF, reduction in dose , delay in next cycles were decided. A dose reduction by one dose level was performed in any case with the following dose-limiting toxicities: absolute neutrophil count (ANC) < 0.5 × 10^9 /L for >7 days, ANC < 0.1 × 10^9 /L for >3 days, grade 3 or 4 thrombocytopenia for >7 days, increase of transaminase by e"50%, severe (grade 3 or 4) mucositis, neuropathy, myalgia or arthralgia not responding to symptomatic treatment. A dose delay was performed in cases with infectious diseases, delayed recovery from infection or febrile neutropenia. The toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0 Characteristics. Informed consent was obtained for all patients. Toxicities, dose reduction and delay, G-CSF use between the two groups were compared using Mann-Whitney test and Fisher2 s exact test. A *P* value < 0.05 was considered as significant.

Results: Table-1 describes the tumour and patients characteristic in detail and Table – 2 about the hormone receptor, Her-2/neu expression. All patients received chemotherapy completely described in Materials and Methods besides side effects. Overall, the mean age and BMI was 48.6 (range from 30 to 74) and 23.9 (range from 18.3 to 32.4), respectively. Older aged patients suffered from fatigue(P=0.008) ,pain (P=0.004) and anaemia (P=0.003) frequently ,and febrile neutropenia associated with mainly low BMI patients. The mean age of the patients in the TAC and ACP group were 40.1±5.8 (range from 30 to 53) and 54.4±8.5 (range from 37 to 74), respectively (*P*<0.001). The mean BMI of the two groups were 22.4±2.8 and 24.7±3.1, respectively (*P*=0.009). The histologic grade (*P*=0.023), nuclear grade (*P*=0.045) and hormonal receptor (ER/ PR) (*P*=0.011) of the two groups were significantly different.

Table 1: Patient demographics and tumors characteristics

		AC-P (n=40)	AC-D (n=40)	P value
1	Age (range)	52 ± 9 (35-71)	42 ± 5.3 (31.4-52.6)	<0.001
2	Body mass index (range)	24.2 ± 3.4 (17.4-31.0)	22.4 ± 2.8 (19-29.1)	0.009
3	Histology (%)IDC ≠ LIC * LDC +ILC Others	31(88.6) 2(5.7) 2(5.7) 0	13(68.4) 2(10.5) 1(5.3) 3(15.8)	NS#
4	Lymph node metastasis	34(94.1)	19(100)	NS#
5	TNM II stage (%) lb lla llb llla lllc	3(11.5) 10(28.6) 7(20.0) 11(31.4) 4(11.4)	1(5.3) 8(42.1) 4(21.1) 1(5.3) 5(26.3)	
6	Operation mastectomy	8(22.9)	3(15.8)	NS#
7	Breast conserving surgery	27(77.1)	16(84.2)	

ACP *, adriamycin, cyclophosphamide, paclitaxel regimen: TAC ^«, adriamycin, cyclophosphamide, docetaxel regimen: IDC "", invasive ductal carcinoma: ILC **, invasive lobular carcinoma: TNMII, tumor node, metastasis

Table 2 : Hormone receptor and Her -2/neu expression

		AC-P (n=40)	AC-D (n=40)	P value
1	Hormone receptor (%) ER ≠/PR§ (+/+)	27(77.1)	8(42.1)	0.011
2	ER ≠/PR§ (+/-)	3(8.6)	1(5.3)	
3	ER ≠/PR§ (-/-)	5(14.3)	10(52.6)	
4	Her -2/neu II (%) (-) +1 +2 +3	25(71.4) 5(14.3) 3(8.6) 2(5.7)	12(63.2) 7(36.8) 0 0	NS**

ACP *, adriamycin, cyclophosphamide, paclitaxel regimen: TAC ^«, adriamycin, cyclophosphamide, docetaxel regimen: ER‟, oestrogen receptor: PR§ , progesterone receptor: Her-2/neuII, human epidermal growth factor receptor -2/neu: NSII, not significant

Table-3 lists the incidence and severity of toxicity by treatment protocol. For non-hematologic toxicity, patients in the TAC group experienced alopecia more frequently than those in the ACP group. Patients in the ACP group experienced peripheral neuropathy (P=0.025) (excluding grade 0/1), nausea (P=0.033) (all grades) more frequently than those in TAC. One patient in the ACP group had transient, reversible renal function impairment. In the hematologic toxicity, grade 2/3/4 neutropenia was more common in the TAC group (n=18, 94.7%) but this was not significant. Febrile neutropenia occurred in 11 (57.9%) and five (14.3%) patients in the TAC and ACP group, respectively (P=0.001). G-CSF use was performed on 24(68.6%) and 18(94.7%) patients in the ACP and TAC group, respectively (P<0.001) (Table-4). On the other hand, anemia was not significantly more common in the TAC group. Two and four patients in the TAC and ACP group, respectively, experienced grade 2/3/4 thrombocytopenia. Dose reduction (one level dose) was performed in 6(17.1%) and 12(63.2%) patients in the ACP and TAC group, respectively (P=0.001) (Table-4). Dose delay was performed in five (14.3%) and two (10.5%) patients in the ACP and TAC group, respectively. Among them, four patients had a dose delay due to an increase in the transaminase level and each of the others had dose delay due to influenza, delayed recovery from febrile neutropenia and knee cellulites respectively. A dose reduction only was significant (P= 0.001).

Table 3 : Toxicities that occurred or worsened during treatment

		AC-P (n=40)	AC-D (n=40)
1	**Hematologic**		
	Neutropenia	32(91.4)	18(94.7)
	Febrile neutropenia	5(14.3)	11(57.9)
	Anemia	13(37.1)	11(57.9)
	Leukopenia	29(82.9)	18(94.7)
	Thyrombocytopenia	5(14.3)	2(10.5)
2	**Nonhematologic**		
	Alopecia	16(45.7)	11(57.9)
	Anorexia	3(8.6)	1(5.3)
	Nausea	1(2.9)	0
	Stomatitis	0	0
	Diarrhea	0	0
	Myalgia/arthralgia	1(3.8)	0
	Peripheral	14(40.0)	2(10.5)
	neuropathy	2(5.7)	1(5.3)
	Gatigue		
3	**Metabolic/laboratory**		
	Alkaline	0	0
	phosphatase	0	0
	Bilirubin	3(8.6)	1(5.3)
	AST	4(11.4)	1(5.3)
	ALT§	1(2.9)	0
	Creatinine	1(2.9)	0
	CcrII		

ACP*, adriamycin, cyclophosphamide, paclitaxsel regimen, TAC ^«,adriamycin, cyclophosphamide, docetaxel regimen: AST‟ , asparatate aminotransferase: alanine aminotransferase: CcrII, creatinine clearance: NS*, not significan.

Table 4 : Dose reduction, delay and G-CFS use

		AC-P (n=40)	AC-D (n=40)	P value
1	Dose reduction (%)	6(17.1)	12(63.2)	0.001
2	Dose delay (%)	5(14.3)	2(10.5)	NSII
3	G-CSF≠ use (%/average ± SD§)	24(68.6/1.35 ± 0.48)	18 (94.7/ 4.39 ±4.06)	<0.001

ACP*, adriamycin, cyclophosphamide, paclitaxel regimen: TAC , adriamycin, cyclophosphamide, docetaxel regimen: G-CSF‟ , granulocyte colony stimulating factor: SD§ , standard deviation: NSII, not significant.

Discussion

Judgement regarding chemotherapy in ca breast varies with patients characteristics and chemotherapy induced toxicity must pay attention in every patient. Total 17 trials showed taxanes (docetaxel and paclitaxel) administration with improved efficacy, and the ECOG 1199 trial is one of them. [7] Overall survival (OS) slightly improved for the weekly paclitaxel and every-3-week docetaxel arm as compared to 3 weekly paclitaxel.[5] Besides being a very wonderful discovery in clinical practice, taxanes group having significant spectrum of toxicity.[6] In several trials including ECOG 1199, docetaxel associated with risk of mortality in patients with abnormal liver function test , frequent neutropenia, severe hypersensivity reactions, fluid retention(patients complains of swelling in body) other toxicities that occurred frequently in docetaxel than paclitaxel are anemia,frequent blood transfusions,nail disorders ,dermatological toxicity,decreased platelate count,infections,administration of growth factors.[5],[7],[8] Bone marrow suppression was serious event in trials of taxanes-chemotherapy. Grade 3 and 4 neutropenia develops in more than 90% of patients and around 40% patients suffer from febrile neutropenia . [9],[10] North american and European guidelines recommend the prophylactic use of growth factors in patients suffer from risk of FN (febrile neutropenia) more than 20%. [11] Docetaxel was associated with less nausea and vomiting. Paclitaxel was associated with more peripheral neuropathy and hypersensitivity reactions. The primary target of taxanes-induced peripheral neuropathy (TIPN) is controversial. Studies in preclinical models demonstrated that the administration of paclitaxel resulted in the accumulation of microtubules in Schwann cells and axons of the sciatic nerve. The main occurrence of distal loss of sensation in the large fibers would suggest that a “dying back” process starting from the distal nerve endings followed by effects on Schwann cells, neuronal body or disturbed axonal transport changes in the affected neurons is the mechanism of TIPN. [12] The incidence and severity of TIPN in paclitaxel is higher than that in docetaxel. [13] For the symptomatic management of TIPN, amitriptyline, glutamine, low-dose oral prednisone and gabapentin have been used with some measure of success for reducing pain, myalgia and arthralgia. [12]

Neutropenic events are associated with higher age, higher body surface area, lower body mass index, regimen type, and more planned chemotherapy cycles. [14] Obese patients Overweight patients are less likely to experience cycle delays due to prolonge There is no evidence that use of actual body weight to determine chemotherapy doses is associated with greater myeloid or non-myeloid toxicity.2, 7-12 Moreover, receipt of full weight-based doses appears to be required for patients, particularly those with estrogen receptor-negative tumors, to achieve the full benefit of chemotherapyd myelosuppression, particularly toward the end of the treatment course. Overall, obese patients are in fact less likely to suffer hematologic toxicity. Healthy older patients without comorbidity had a higher rate of hematologic toxicity than younger patients, but no increase

in nonhematologic toxicity. [15],[16] Younger patients as well as in elderly patients ,taxanes are prescribed in adjuvant and neoadjuvant setting. Both age group received the same advantages but keeping in mind that older age suffer from more toxicity and mortality . [16] Consistent with the two trials, in the present study, increasing age was associated with an increased risk of anemia (P=0.004), fatigue (P=0.009) and pain (P=0.003), and a decreasing BMI was associated with an increased risk of febrile neutropenia (P=0.009) (data not shown).

In one analysis which evaluating RTDI (Relative total dose intensity) ,shows that chemotherapy dose reduction and delay decreases RTDI, and give negative impact on short- and long-term outcome in advanced and metastatic breast cancer (MBC) patients .[17] Dose delay and reduction of taxanes in ca breast lead to decrease overall survival in patients with more dose reduction and dela. This study was of very short follow up , so longterm outcomes were not calculated .

In conclusion, both taxane have different toxicity spectrum , and all of them two main toxicity were febrile neutropenia (docetaxel), and peripheral neuropathy (paclitaxel). Growth factor use and dose reduction frequently used in AC-D group as compared to AC-P group. Taxanes should be selected in advanced breast cancer, keeping in attention toxicity profile and patient need. And a proper selection of taxane-based regimen balances the quality of life and disease control. However dose delay and reduction should be done when intolerable toxicity deteriorating quality of life.

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