Original Article

The safety and tolerability of FE_{100}C-D chemotherapy in a non-trial population of node positive breast cancer compared to PACS-01 trial group; Salmaniya Medical Complex experience

Aysha Seddiq AL Zaman, Yahya S. AL Zaman[1], Entisar S. AL Zaman[2]

Departments of Oncology and Hematology, [2]Obstetrics and Gynaecology, Salmaniya Medical Complex, Manama, [1]Department of Endocrinology and Internal Medicine, Bahrain Defence Force Hospital, West Riffa, Kingdom of Bahrain

ABSTRACT

Introduction: In our institution, adjuvant taxanes are currently offered to fit node-positive breast cancer patients who are either Her2 positive (any ER/PR) or triple negative (ER/PR/Her2 negative). The FE_{100}C-D (FE100C × 3 → docetaxel 100 mg/m² × 3) regime, based on the PACS 01 trial1 is used. **Materials and Methods:** We retrospectively audited our experience with FE_{100}C-D at Salmaniya Medical Complex. Over a 2-year-period, 100 patients commenced adjuvant FE100C-D chemotherapy. Data was matched with the FE_{100}C-D arm of the PACS 01 trial. **Results:** Median age was 54 years. Twenty-six patients (26%) had ≥1 episode of febrile neutropenia (FN), including one fatal episode; 29% patients required treatment interruption ≥1 week; 30% patients had dose reductions; and 30% patients received < 90% dose intensity of docetaxel. **Conclusion:** The FN rate was substantially higher and docetaxel dose intensity substantially lower in our unselected sample of patients than in the trial population, this "real-life" data demonstrates the problems of applying clinical trial data to the more generalised patient population. Meanwhile, the routine use of prophylactic G-CSF support with this protocol is warranted.

Key words: Breast cancer, docetaxel, febrile neutropenia, FEC_{100}-D, toxicity

INTRODUCTION

In recent years, a number of clinical trials have addressed the role of taxanes in addition to anthracycline-based chemotherapy in the adjuvant treatment of node-positive breast cancer. While the results of these studies are often conflicting, several studies have shown an improvement in disease-free and overall survival for anthracycline–taxane combinations, albeit at the cost of increased toxicity.[1-8] One such trial is PACS 01[1], which compared 6 cycles of 5-FU 500 mg/m², epirubicin 100 mg/m², and cyclophosphamide 500 mg/m² (FE_{100}C) with 3 cycles of FE_{100}C, followed by 3 cycles of docetaxel 100 mg/m². Within PACS 01, the taxane-containing regimen led to 5% improvement in disease-free survival and a 4% improvement in overall survival with an acceptable toxicity profile. We audited our experience with this regime at our major tertiary referral centre looking at the toxicity of this regime in an unselected population.

Access this article online	
Quick Response Code:	Website: www.ccij-online.org
	DOI: 10.4103/2278-0513.119261

MATERIALS AND METHODS

All patients commencing adjuvant FE_{100}C-D chemotherapy at a regional cancer centre (Salmaniya Medical Complex) between 1st January 2007 and 31st December 2008 were included in this retrospective audit. In both centers, patients with breast cancer receiving adjuvant FE_{100}C-D

Address for correspondence: Dr. Aysha Seddiq Al Zaman, PO Box 12, Department of Oncology and Hematology, Salmaniya Medical Complex, Manama, Kingdom of Bahrain. E-mail: AZaman@health.gov.bh

were identified from pharmacy records. Clinical data were obtained from the case notes of the treating centre and, wherever possible, any other hospital to which a patient was admitted. Data was then compared with that from the FE_{100}C-D arm of the PACS 01 trial.[1]

RESULTS

Patient characteristics

A total of 100 patients were treated at Salmaniya hospital between January 2007 and December 2008. Median age of patients was 54 years (range 30-65 years). Baseline characteristics are summarized in Table 1 for both the study group and the FE_{100}C-D arm of the PACS 01 trial, and it clearly shows that, similar to the Pac-1 population, patient treated in our institution with this regimen were high-risk group of patients as was demonstrated by the following Figures: 74% of patients had tumors greater than 2 cm, 78% Grade 111, 97% node-positive, 58% ER and PR negative, and 54% Her-2 positive.

Exposure to treatment and dose intensity

Also, 91% patients completed all 6 planned cycles of adjuvant chemotherapy (3 cycles of FE_{100}C followed by 3 cycles of docetaxel), and, of 600 planned cycles of chemotherapy, 589 were delivered and 33 cycles were delayed, with 29% patients experiencing at least a week's interruption of treatment. Moreover, 30% patients had dose reductions, with 10.5% of chemotherapy cycles in our study being given at a reduced dose. The first cycle to be reduced was cycle 5 (the second cycle of docetaxel) in 21 (70%) of these patients because of significant toxicity from the first dose of docetaxel, and 9% patients stopped treatment before the 5th or 6th cycle. A relative dose intensity of < 90% was seen in 29% of the women on the docetaxel part of the regime, but in only 1% patients on the FE_{100}C part of the regime, and 20% patients received < 85% dose intensity of docetaxel. Dose reductions, delays, and dose intensities are detailed in Table 2 and compared to the reported data from the FE_{100}C-D arm of PACS 01.

Toxicity

Twenty-six patients (26%) had at least one episode of FN, including one fatal episode. There were 30 (30/589 cycles) episodes in total (5%), all leading to hospitalization. Median presentation with FN was on day 9 of the chemotherapy cycle (range days 4-14). Thirteen episodes (43%) occurred following cycle 4 and 17 (57%) episodes occurred following cycles 4-6 (17% of all patients treated). Details of FN episodes are summarized in Table 3.

Eight patients with FN had a dose reduction of the subsequent cycle of chemotherapy and 6 had subsequent cycle delayed (3 patients had both dose reduction and delay of next cycle). One patient had 3 further FN episodes despite G-CSF (3 cycles) and dose reduction (2 cycles). The rest of the dose reductions (53/63 cycles [84%]) and dose delays (28/34 cycles [82%]) were secondary to uncomplicated neutropenia or other reasons [Table 4].

Twenty-three of the 26 patients suffering from FN (88.5%) received G-CSF with all subsequent cycles of chemotherapy. Three patients did not receive subsequent G-CSF. Of

Table 1: Baseline characteristics of patients

	Salmaniya medical complex (*n*=100)		PACS 01 (*n*=1,003)	
	Number	%	Number	%
Breast surgery				
Lumpectomy	33	33	531	52.9
Mastectomy	64	64	472	47.1
Other/unknown	3	3	0	0
Tumor size				
<2 cm	25	25	360	39.1
2-5 cm	64	64	490	53.3
>5 cm	10	10	70	7.6
Other/unknown	1	1	83	8.2
Grade				
1	0	0	126	12.8
2	17	17	430	43.7
3	78	78	385	39.1
Not gradable	3	3	44	4.5
Missing or n/a	2	2	0	0
Nodal status				
1-3 nodes	48	48	626	62.4
≥4 nodes	49	49	377	37.6
n/a or unknown	3	3	0	0
ER/PR				
Positive	40	40	802	80.7
Negative	58	58	192	19.3
Missing	2	2	9	1
Her-2				
Positive	54	54	Unknown	Unknown
Negative	46	46	Unknown	Unknown

Table 2: Exposure to treatment and dose intensity

	Salmaniya medical complex I (*n*=100)		PACS 01 (*n*=1003)	
	No	%	No	%
No treated pts	100		1001	99.8
No cycles delivered	589	98.1	5922	
Women completed 6 cycles	91	91	962	96.1
Treatment delayed, cycles	33	5.6	488	8.2
Treatment delay, no. of pts	29	29	NA	NA
Dose reduction, cycles	62	10.5	47	0.8
Dose reduction, no. of pts	30	30	N/A	N/A
Dose reductions after cycle 5, no. of pts	21	21	NA	NA
Women with rel. dose intensity <90%				
Epirubicin	1	1	151	15.1
Docetaxel	29	29	181	18.1
Women with relative dose intensity <85%				
Epirubicin	0	0	NA	NA
Docetaxel	21	21	NA	NA

Table 3: Febrile neutropenia episodes (*n*=30)

Febrile neutropenia	No. (%) Total no. pts=100 Total no. cycles=589
Number of patients with FN	26 (26)
Number of cycles with FN	30 (5)
FN episode following cycle no	
1	3 (3)
2	3 (3)
3	4 (4)
4	13 (13)
5	2 (2)
6	2 (2)
4-6	17 (17)
Neutropenia grade	
2	2 (7)
3	7 (28)
4	18 (62)
unknown	2 (7)
G-CSF administered during episode	
Yes	9 (31)
No	8 (28)
Unknown	10 (35)
Chemo cycle following FN episode	
Dose delay	3 (10)
Dose reduction	5 (17)
Dose delay and reduction	3 (10)
G-CSF	26 (87)

Table 4: Causes for dose delays and reductions

	Number of patients*
Reasons for dose reductions	
Febrile neutropenia	6
Lethargy	3
Mucositis	9
Diarrhoea	2
Skin toxicity	2
Infection (non-neutropaenic)	2
Nausea and vomiting	1
Myalgia	3
Prev chemo	1
Unknown	1
Reasons for dose delays	
Non-febrile neutropenia	11
Febrile neutropenia	4
Diarrhea	2
Infection (non-neutropenic)	13
Unknown	2

*Many patients had more than one reason for their treatment being dose reduced

these, 1 patient had died as a result of FN, 1 received dose reduction and delay before proceeding with further chemotherapy, and 1 proceeded to first cycle docetaxel with no G-CSF.

Case records were available from the admitting hospital for 24/30 episodes. Patients were referred for admission through a number of routes: Their general practitioner (9 cases), self-referral (10 cases), chemotherapy nurses (1 case), or not documented (10 cases). There were documented positive blood cultures in 3 episodes, 2 of these were *Clostridium difficile* (including 1× fatal episode) and 1 was *Escherichia coli*. Negative blood culture results were obtained in 14 further episodes with this information being unavailable for the rest of the group. The median duration of hospitalization was 6 days (range 1-12 days, data missing for 6 episodes).

DISCUSSION

Only a small fraction of patients with breast cancer are included in clinical trials, with eligibility and exclusion criteria generally selecting a good performance status group with minimal co-morbidities. This makes it likely that trial patient cohorts are not representative of the patient population as a whole. Moreover, little is known about the outcomes when clinical trial results are extrapolated and applied to a general population of patients. In this study, we have reported the outcomes of a general adjuvant breast cancer population group referred to our centre (Tertiary Cancer Centre) who might be expected to benefit from FE_{100}C-D chemotherapy. We compared this group to the FE_{100}C-D chemotherapy arm of the PACS 01 trial. We believe that this study is one of the first to definitively report on toxicities suffered by a group of patients drawn from a general breast cancer population and treated with a study arm chemotherapy regime and to compare these toxicities with those seen within the trial.

Patients were selected based on their pathology: All were node positive with either Her2 positivity or triple negative disease. These criteria were based on the limited and flawed retrospective subset analysis data from a number of taxane containing trials, which suggested that, if any group benefited from taxanes, then it would seem to be those who were node positive with either Her2 positivity or triple negative disease.[2,6,8] All patients had a performance status (PS) of 0 or 1, which matched PACS 01, where patients had to be PS < 2. Overall, our patient group was slightly older (median age 54 vs. 50 years) than the FE_{100}C-D group within PACS 01. Analysis of this demonstrated that 8 patients (8%) were aged between 65 and 70 years and would have been ineligible for entry into the PACS 01 trial on this basis. Removing these 8 patients gave a median age of 53 years.

Our patient cohort had worse prognosis disease, with substantially more patients having grade 3, T2 or T3 disease, and ≥4 positive nodes. Also, of note is the significant difference in oestrogen receptor status between our group and that within PACS 01 [Table 1]. This reflects the local eligibility criteria within our centre for adjuvant taxanes, which excludes ER-positive patients unless also HER-2 positive. HER-2 positivity did not feature in the inclusion criteria for PACS 01. Despite these differences, as already highlighted, all our patients were performance status (PS) 0-1, and thus although we might expect their long-term prognoses to differ from that seen within the trial, we would not expect any effect from these pathological

differences to impact on treatment tolerance or toxicities. Clearly, however, a significantly higher morbidity was seen in our patient cohort, particularly in association with the docetaxel part of the regime, than what had been expected given the PACS 01 trial results. Similarly, the number of patients failing to achieve ≥90% dose intensity was higher than expected at 30% as compared with 18.1% seen in PACS 01. It could be argued that inclusion of older patients who, despite good performance status, may be more likely to suffer toxicities including FN, could be skewing these figures. However, exclusion of these patients (three of whom experienced an episode of FN) still left a FN rate of 25% (23 patients with one or more FN episodes of a total of 92 patients aged 64 or less). The inclusion of older patients in our patient group therefore did not significantly increase the incidence of FN.

Twenty-six patients (26%) in our group suffered a total of 30 episodes of FN. Seventeen (56.7%) of these episodes occurred in 15 patients (15%) within cycles 4-6. Therefore 65% of patients (15 of 26) who suffered a FN episode suffered this within cycles 4-6. Within PACS 01, 11.2% suffered an episode of FN with 7.4% of patients having an episode occurring within cycles 4-6. Thus, twice as many patients suffered an episode of FN secondary to docetaxel as compared to the trial data. This is similar to audit data from other centers published in abstract form[9-11] and also a recent letter publication regarding real-life experience using the docetaxel/cyclophosphamide regimen.[12] A suggested mechanism for this is late neutrophil nadir associated with $FE_{100}C$ in conjunction with the early neutropenia, which occurs with docetaxel. This, however, might reasonably have been expected to be evident in the trial patient population. Since our patient cohort were of identical PS to that included in PACS 01 and adjustment for age still left a significantly higher FN rate, it left us to conclude that co-morbidities and concomitant medications play a significant role. ASCO guidelines state that a FN rate of ≥ 20% should lead to the provision of primary prophylaxis with colony stimulating factors (CSF).[13] This has led our centre to change practice with granulocyte colony stimulating factor (G-CSF), which is now being prescribed as primary prophylaxis in all cycles for all patients receiving the $FE_{100}C$-D regime.

Overall, $FE_{100}C$ was tolerated well with the dose intensity achieved being comparable to that seen within PACS 01. However, 30% of our patients received <90% dose intensity of docetaxel because of a combination of dose reductions and/or dose delays and 21% received <85% dose intensity of docetaxel. The majority of these dose modifications were driven by episodes of uncomplicated neutropenia or mucositis [Table 4]. Clearly, FN, because of the associated risk of mortality, is of significant concern. However, the prescription of G-CSF for cycles of treatment subsequent to a FN episode seemed to largely neutralize FN as an ongoing toxicity and to avoid the need for dose modifications secondary to this. The decision therefore to dose reduce or dose delay chemotherapy was secondary in most cases to non-FN toxicities and thus would not be altered by the addition on G-CSF. This also suggests that primary prophylaxis with G-CSF alone may not improve the numbers of patients failing to achieve > 90% dose intensity. Adequate treatment and prevention of other toxicities would also be required.

Stringent eligibility criteria true of most trials means that the included patients are almost invariably not representative of the general patient population.[14] Published data on this subject is scant, however, it seems obvious that when a regime of treatment is given to a less selected population, it is likely that a greater range and severity of toxicities may be seen. In our review, this has proved to be the case, with toxicities in the form of FN being significantly greater than that quoted in the trial and, in one case, leading to toxic death.

It is of note that the greater than anticipated incidence of all toxicities led to a substantial number (30%) of patients failing to achieve >90% dose intensity in the docetaxel arm. This is likely to reduce the effectiveness of this treatment and may negate any potential long-term benefit in terms of disease-free or overall survival over and above standard treatments, which are recognized to be less toxic.

CONCLUSION

FEC-100-D protocol is less well tolerated in real-life patients and is associated with higher serious toxicities, namely FN as compared to highly selected population treated within clinical trials. These results should lead to tempering of the direct transfer of trial-based treatments to the general population. Similarly, they raise the question of whether trial populations should be more typical of the general population. It would be prudent on introduction of any new chemotherapy regime to a centre's routine "off-study" treatment program for a prospective audit of toxicity and dose intensity and comparison of this with the initiating trial data to be mandatory. Should these results vary significantly from that of the initiating trial, then concerns should be raised regarding whether the suggested longer term outcome benefits will be achieved in this less-selected population, whether these likely reduced benefit levels outweigh the increased toxicities, and whether more stringent patient selection criteria are required in this general population. Therefore, we plan to continue following this general patient group and report their outcomes in comparison to the reported PACS 01

trial outcomes. Meanwhile, routine use of prophylactic G-CSF support for all patients to be treated with this chemotherapeutic regime is highly recommended.

REFERENCES

1. Roche H, Fumoleau P, Spielmann M, Canon JL, Delozier T, Serin D, *et al*. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: The FNCLCC PACS 01 Trial. J Clin Oncol 2006;24:5664-71.
2. Henderson IC, Berry DA, Demetri GD, Cirrincione CT, Goldstein LJ, Martino S, *et al*. Improved outcomes from adding sequential paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21:976-83.
3. Mamounas EP, Bryant J, Lembersky B, Fehrenbacher L, Sedlacek SM, Fisher B, *et al*. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28. J Clin Oncol 2005;23:3686-96.
4. Buzdar AU, Singletary SE, Valero V, Booser DJ, Ibrahim NK, Rahman Z, *et al*. Evaluation of paclitaxel in adjuvant chemotherapy for patients with operable breast cancer: Preliminary data of a prospective randomized trial. Clin Cancer Res 2002;8:1073-9.
5. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, *et al*. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-9.
6. Martin M. Docetaxel, doxorubicin and cyclophosphamide (the TAC regimen): An effective adjuvant treatment for operable breast cancer. Womens Health (Lond Engl) 2006;2:527-37.
7. Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S, *et al*. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 2006;24:5381-7.
8. Ellis P, Barrett-Lee P, Johnson L, Cameron D, Wardley A, O'Reilly S, *et al*. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): An open-label, phase III, randomised controlled trial. Lancet 2009;373:1681-92.
9. Head J, Archer C, Harper-Wynne C. Rates of neutropaenic sepsis with the use of adjuvant FEC100-docetaxel (FEC100-T) chemotherapy in high-risk node-positive patients with early breast cancer; a UK perspective. NCRI Cancer Conference 2008; Poster B64.
10. Ali Z, O'Reilly S, Zahoor T. Experience of febrile neutropaenia and secondary G-CSF prophylaxis during FEC-D chemotherapy in Merseyside and Cheshire Cancer Network. NCRI Cancer Conference 2008; Poster B67.
11. Gohil S, Sharma A, Harper-Wynne C. Comparison of rates of febrile neutropaenia using FEC100/Docetaxel100 chemotherapy in breast cancer patients with and without primary GCSF prophylaxis. NCRI Cancer Conference 2009;Poster B75.
12. Gohil S, Sharma A, Harper-Wynne C. Comparison of rates of febrile neutropaenia using FEC100/docetaxel100 chemotherapy in breast cancer patients with and without primary GCSF prophylaxis. NCRI Cancer Conference 2009; Poster B75.
13. Smith TJ, Khatcheressian J, Lyman GH. 13. 2006 Update of ASCO practice guideline recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187-205.
14. Cottin V, Arpin D, Lasset C, Cordier JF, Brune J, Chauvin F, *et al*. Small-cell lung cancer: Patients included in clinical trials are not representative of the patient population as a whole. Ann Oncol 1999;10:809-15.

Cite this article as: AL Zaman AS, AL Zaman YS, AL Zaman ES. The safety and tolerability of FE 100 C-D chemotherapy in a non-trial population of node positive breast cancer compared to PACS-01 trial group; Salmaniya Medical Complex experience. Clin Cancer Investig J 2013;2:202-6.

Source of Support: Nil, **Conflict of Interest:** No.