EUROPEAN JOURNAL OF CANCER 47 (2011) 215–220

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Are patients in clinical trials representative of the general population? Dose intensity and toxicities associated with $FE_{100}C$-D chemotherapy in a non-trial population of node positive breast cancer patients compared with PACS-01 trial group

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ARTICLE INFO

Article history:
Received 8 April 2010
Received in revised form 30 September 2010
Accepted 8 October 2010
Available online 18 November 2010

Keywords:
Breast cancer
Docetaxel
Febrile neutropaenia
Toxicity

ABSTRACT

Purpose: 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 ($FE_{100}C \times 3 \rightarrow$ docetaxel 100 mg/m^2 $\times 3$) regime, based on the PACS 01 trial[1] is used. We retrospectively audited our experience with $FE_{100}C$-D at The Beatson West of Scotland Cancer Centre and one representative district general hospital (DGH), Falkirk and District Royal Infirmary (FDRI).

Patients and methods: Over a two year period, 101 patients commenced adjuvant $FE_{100}C$-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 $\geqslant 1$ episode of febrile neutropaenia (FN), including one fatal episode. Twenty-nine percent of patients required treatment interruption $\geqslant 1$ week. Thirty percent of patients had dose reductions. Thirty percent of 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 reference study.[1] This 'real-life' data illustrates the problems of applying clinical trial data to the more generalised patient population.

1. 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. Whilst the results of these studies are often conflicting, several 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 which compared 6 cycles of 5-FU 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2 ($FE_{100}C$) with 3 cycles of $FE_{100}C$ followed by 3 cycles of docetaxel 100 mg/m^2. Within PACS 01 the taxane containing regimen led to a 5% absolute improvement in disease free survival and a 4%

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.10.001

absolute improvement in overall survival with an acceptable toxicity profile which is clearly clinically significant. This regimen was adopted for use in our regional centre and district hospitals in patients with node positive breast cancer who were performance status 0 or 1. Based on limited and conflicting evidence regarding the patient population who might derive the most benefit, use was restricted to those who were either HER2 positive or oestrogen receptor (ER), progesterone receptor (PR) and HER2 receptor negative. We audited our experience with this regime at our major tertiary referral centre and at one representative DGH, looking at the toxicity of this regime in an unselected population who fulfilled the above criteria.

2. Patients and methods

All patients commencing adjuvant $FE_{100}C$-D chemotherapy at a regional cancer centre (The Beatson West of Scotland Cancer Centre) and a district general hospital (Falkirk and District Royal Infirmary) between 1st January 2006 and 31st December 2007 were included in this retrospective audit. In both centres, patients with breast cancer receiving adjuvant $FE_{100}C$-D were identified from pharmacy records. Clinical data were obtained from the case notes of the treating centre and, where 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] Toxicity was graded using Common Toxicity Criteria v.2 which match the World Health Organisation (WHO) criteria used to report toxicity in the PACS 01 trial. Those patients who were confirmed to be Her2 positive were subsequently treated with Trastuzumab as per the HERA trial 1 year data.[9]

3. Results

3.1. Patient characteristics

One hundred and one patients in total were treated at the 2 hospitals between January 2006 and December 2007, 75 in the cancer centre and 26 at the DGH. Median age was 54 years (range 30–70 years). Baseline characteristics are summarised in Table 1 for both the study group and the $FE_{100}C$-D arm of the PACS 01 trial. All patients adhered to the same haematological entry criteria as PACS 01 and all had normal MUGA scan results pre-chemotherapy. Fifteen patients would have been ineligible for PACS 01 based on age $\geqslant$65 years (8 patients), previous cancer diagnosis (7 patients, 5 of whom received chemotherapy for their previously diagnosed cancer)

Table 1 – Baseline characteristics of patients.

	BWoSCC/FDRI[a] (n = 101)		PACS 01 (n = 1003)	
	Number	%	Number	%
Breast surgery				
Conservation	32	32	531	52.9
Mastectomy	65	64	472	47.1
Other/unknown	4	4		
Tumour size				
$\leqslant$2 cm	30	30	360	39.1
2.1–5 cm	58	58	490	53.3
>5 cm	10	10	70	7.6
Other/unknown	3	2	83	
Grade				
1	0	0	126	12.8
2	18	18	430	43.7
3	78	77	385	39.1
Not gradable	n/a	n/a	44	4.5
Missing or n/a	3	3		
Mixed grade 2/3	2	2		
Nodal status				
0 nodes	3	2		
1–3 nodes	50	50	626	62.4
$\geqslant$4 nodes	46	46	377	37.6
n/a or unknown	2	2		
ER/PR				
Positive	43	43	802	80.7
Negative	58	57	192	19.3
Missing			9	
Her-2				
Positive	53	52	Unknown	Unknown
Negative	48	48	Unknown	Unknown

[a] BWoSCC – Beatson West of Scotland Cancer Centre; FDRI – Falkirk and District Royal Infirmary.

or node negativity (3 patients). One patient had both a previous cancer diagnosis and age ⩾65 years, two patients had previous cancer diagnosis and node negative disease.

3.2. Dose intensity

Ninety-two percent of 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, 590 were delivered. Thirty-four cycles were delayed, with 29% of patients experiencing at least a week's interruption of treatment. Thirty percent of patients had dose reductions, with 10.7% 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, due to significant toxicity from the first dose of docetaxel. Seven percent of patients stopped treatment before the 5th or 6th cycle. A relative dose intensity of <90% was seen in 30% of the women on the docetaxel part of the regime but in only 1% of patients on the $FE_{100}C$ part of the regime and 21% of patients received <85% dose intensity of docetaxel. Excluding patients who would have been ineligible for PACS 01 on grounds of age ⩾65 years, node negativity or previous cancer diagnosis led to a relative dose intensity of <90% in 26% of women on the docetaxel part of the regime and 20% received less than 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.

3.3. Toxicity

Twenty-six patients (26%) had at least one episode of FN, including one fatal episode. There were 30 (30/590 cycles) episodes in total (5%), all leading to hospitalisation. Median presentation with FN was on day 9 of the chemotherapy cycle (range day 4–14). Due to the geography of the area patients could be admitted to the cancer centre ($n = 7$), the DGH (FDRI) ($n = 11$) or their own local DGH hospital ($n = 12$). Fourteen episodes (47%) occurred following cycle 4 and 17 (57%) episodes occurred following cycles 4–6 (17% of all patients treated). Details of FN episodes are summarised in Table 3.

Four patients with FN had a dose reduction of the subsequent cycle of chemotherapy, 5 had the subsequent cycle delayed and 2 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 neutropaenia or other toxicities (Table 4).

In 26 of 30 episodes (87%) G-CSF was given on the subsequent cycle of chemotherapy. G-CSF was administered at a dose of 300 μg subcutaneously per day for a median duration of 10 days (range 5–10) usually being commenced on day 5 (range day 2 to day 8). Four patients did not receive G-CSF on the cycle following an episode of febrile neutropaenia. Of these, 1 had died as a result of febrile neutropaenia, 1 had grade 4 mucositis as well as FN and received a dose reduction and delay before proceeding with further chemo, 1 had the episode of FN following $FE_{100}C$ and proceeded to first cycle docetaxel with no G-CSF as per protocol at that time, and 1 had FN on cycle 6 so there was no further cycle of chemotherapy.

Case records were available from the admitting hospital for 25/30 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 e-coli. Negative blood culture results were obtained in 23 further episodes, 1 episode had no blood culture taken, 1 had a necrotic wound explored and implant removed, 2 further episodes had no blood culture results available. The median duration of hospitalisation was 6 days (range 1–12 days, data missing for 6 episodes). G-CSF was administered during the FN episode in 13 cases, not administered in 11 cases and in 6 cases no documentation was available to confirm whether G-CSF was administered or not. Twenty five episodes were treated with broad spectrum antibiotic cover (tazocin/gentamicin in most cases) until recovery or cultures came back positive to guide antibiotic use. In 5 episodes the information could not be found.

Table 2 – Exposure to treatment.

	BWoSCC/FDRI ($n = 101$)		PACS 01 ($n = 1003$)	
	Number	%	Number	%
No. treated patients	101		1001	
No. cycles delivered	590	98.3	5922	
Women completed 6 cycles	92	92	962	96.1
Treatment delayed, cycles	34	5.8	488	8.2
Dose reduction, cycles	63	10.7	47	0.8
Dose reduction, No. of patients	30	30	N/A	N/A
Women with rel. dose intensity <90%				
Epirubicin	1	1	151	15.1
Docetaxel	30	30	181	18.1
Women with relative dose intensity <85%				
Epirubicin	0	0		
Docetaxel	21	21		

Table 3 – Febrile neutropaenia (FN) episodes (n = 30).

Febrile neutropaenia	No. (%) Total No. patients = 101 Total No. cycles = 590	PACS 01 data % Of patients (n = 1001)
Number of patients with FN	26 (26)	
Number of Cycles with FN	30 (5)	11.2
FN episode following cycle No.:		
1	4 (4)	
2	4 (4)	
3	5 (5)	
4	14 (14)	4.6
5	2 (2)	2.3
6	1 (1)	1.2
4-6	17 (17)	7.4
Neutropaenia grade		
2	1 (3)	
3	6 (20)	
4	23 (77)	
G-CSF administered during FN episode		
Yes	13 (43)	
No	11 (37)	
Unknown	6 (20)	
Chemo cycle following FN episode		
Dose delay	4 (13)	
Dose reduction	5 (17)	
Dose delay and reduction	3 (10)	
Prophylactic G-CSF	26 (87)	

4. 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 and linked District General Hospital) who might be expected to benefit from $FE_{100}C$-D chemotherapy. We have compared this group to the $FE_{100}C$-D chemotherapy arm of the PACS 01 trial.[1] We believe 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 compare those toxicities with those seen within the trial.

Patients were selected based on their pathology: 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] Of our patient cohort 97% were node positive with either Her2 positivity or triple negative disease. Three patients were node negative, two of whom had received previous chemotherapy for breast cancer which led to the choice of $FE_{100}C$-D chemotherapy in this instance. All three node negative patients were triple negative. Patients all 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 versus 50 years) than the $FE_{100}C$-D group within PACS 01. Analysis of this demonstrated that eight 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 eight 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 $\geqslant$4 positive nodes. Also of note is the significant difference in oestrogen receptor status between our group and that within PACS 01 (see 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 substantially higher morbidity was seen in our patient cohort, particularly in association with the docetaxel part of the regime, than had been expected given the PACS 01 trial results. Similarly the number of patients failing to achieve a $\geqslant$90% dose intensity was higher than expected at 30% compared with 18.1% seen in PACS 01.

Twenty-six patients (26%) in our group suffered a total of 30 episodes of FN. Seventeen (56.7%) of these episodes

Table 4 – Causes for dose delays and dose reductions.

	Number of patients[a]
Reasons for dose reductions	
Febrile neutropaenia	6
Grade 4	
Grade 3	0
Lethargy	3
Mucositis total number	9
Grade 2	2
Grade 3	4
Grade 4	0
Grade unknown	3
Diarrhoea total number	4
Grade 3	2
Grade 4	1
Grade unknown	1
Skin toxicity grade 3/4	2
Infection (non-neutropaenic)	2
Nausea and vomiting	1
Myalgia	3
Prev chemo	1
Unknown	1
Reasons for dose delays	
Non-febrile neutropaenia total number	11
Grade 2	5
Grade 3	4
Grade 4	1
Grade unknown	1
Febrile neutropaenia total number	6
Grade 2	0
Grade 3	4
Grade 4	2
Grade unknown	0
Diarrhoea	3
Infection (non-neutropenic)	13
Unknown	2

[a] Many patients had more than one reason for their treatment being dose reduced or dose delayed.

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 compared to the trial data. This is similar to audit data from other centres published in abstract form[10–12] and also a recent letter publication regarding real-life experience using the docetaxel/cyclophosphamide regimen.[13] A suggested mechanism for this is the late neutrophil nadir associated with $FE_{100}C$ in conjunction with the early neutropaenia which occurs with docetaxel. This, however, might reasonably have been expected to be evident in the PACS 01 trial patient population.

ASCO guidelines state that a FN rate of 20% or more should lead to the provision of primary prophylaxis with colony stimulating factors (CSF).[14] This has led our centre to change practice with granulocyte colony stimulating factor (G-CSF) 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 $FE_{100}C$-D arm. However, 30% of our patients received less than 90% dose intensity of docetaxel due to a combination of dose reductions and/or dose delays and 21% received less than 85% dose intensity of docetaxel, a substantially higher percentage than was reported in PACS-01. Of the 15 patients who would have been ineligible for PACS 01 on age, node negativity or previous cancer diagnosis criteria, 60% suffered a dose modification. Exclusion of them from the analysis, however, meant that still 26% of patients received <90% dose intensity and 20% received <85% dose intensity of docetaxel. The majority of these dose modifications were driven by episodes of uncomplicated neutropaenia 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 neutralise FN as an ongoing toxicity and avoid the need for dose modifications secondary to this. The decision, therefore, to dose reduce or delay chemotherapy was secondary, in most cases, to non-FN toxicities and thus would not be altered by the addition of G-CSF. This also suggests that primary prophylaxis with G-CSF alone may not improve the numbers of patients failing to achieve >85% dose intensity. Adequate prevention and treatment of other toxicities would also be required.

It has already been noted that in our cohort, 15 patients failed PACS 01 eligibility criteria (age $\geqslant$65 years, previous diagnosis of breast cancer and/or node negativity). Excluding these 15 patients, however, still left a FN rate of 25% (22 of 86 patients) and a relative dose intensity of <90% in 26% of women on the docetaxel part of the regime, with 20% receiving less than 85% dose intensity of docetaxel. Our patient cohort was of identical PS to that included in PACS 01. Our median age on exclusion of the eight patients ineligible on the basis of age remained at 53 years (and 52 years when all ineligible patients were excluded), which is slightly (but non-significantly) higher than the median age within PACS 01 (50 years). Age, therefore, cannot be completely excluded as a contributory factor. Despite this, however, we must conclude that there is a true difference between trial selected patients and 'real world' patients. This may be due to other unrecorded co-morbidities, concomitant medications or subtle as yet unrecognised differences which lead to poorer tolerance of a trial regime when it is transferred to the general eligible population.

The stringent eligibility criteria of most trials can almost invariably mean that the included patients are not representative of the general patient population.[15] For example, patients with previous diagnoses and treatment of malignancy are excluded from trials but are treated within the general population group. These patients may theoretically experience a greater level of toxicity and skew the results, however, excluding them (albeit from a relatively small sample) did not appear to dramatically improve the toxicities reported nor the dose intensities achieved as highlighted above. Published data on this subject is scant, however, it seems likely that when a regime of treatment is given to a less selected population 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 quoted in the trial and, in one case, leading to a toxic death. Further study is, however, required.

These results should lead to tempering of the direct transfer of trial based treatments to the general population. The greater than anticipated incidence of all toxicities led to a substantial number of patients failing to achieve a reasonable dose intensity of docetaxel. This may reduce the effectiveness of this treatment and, therefore, negate any potential improvement in long term benefit (disease-free or overall survival) over and above standard treatments which are recognised to be less toxic. Similarly these results 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 programme 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 within the general population.

Clearly the retrospective nature of the data collected in our audit could affect the results we are seeing. It would be preferable to prospectively audit eligibility, toxicities and outcomes of any new regime when initiated in a non-trial population to allow comparison with the original trial data and further to allow judgement of the transferability of that treatment into a general population based patient group. We plan to continue to follow this general patient group and report their outcomes in comparison to the reported PACS 01 trial outcomes.

Conflict of interest statement

N.S. received honoraria payment from Sanofi-Aventis for lecture.

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