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ORIGINAL ARTICLE

TAXTOX – a retrospective study regarding the side effects of docetaxel given as part of the adjuvant treatment to patients with primary breast cancer in Denmark from 2007 to 2009

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Abstract

Background. In 2007 docetaxel was introduced as part of the adjuvant setting offered to high risk breast cancer patients in Denmark. Meta-analyses had shown that taxane-containing chemotherapy reduced the relative risk of relapse and death by 20–30%, apparently with moderate side effects. The treatment was given as three cycles of cyclophosphamide (600 mg/m^2) and epirubicin (90 mg/m^2) followed by three cycles of docetaxel (100 mg/m^2). Because of an apparent high incidence of side effects, especially febrile neutropenia (FN) and non-hematologic side effects, the DBCG (The Danish Breast Cancer Cooperative Group) initiated a retrospective study of adverse reactions to the newly introduced regime and all patients were offered primary prophylaxis with growth factors (G-CSF) pr 1/1-2008. *Material and methods*. Two medical doctors examined available journals and nurse charts from the 13 oncology departments in Denmark, and graded all side effects according to NCI CTC version 2.0. To be enrolled, the patients should have received three cycles of EC and at least one cycle of docetaxel. The side effects were investigated before and after routine use of G-CSF. *Results.* One thousand one hundred and forty-three patients entered the study. In 2007 (before G-CSF) the incidence of FN was 25% and 90.6% of the patients completed the planned treatment. In 2008 (after the introduction of G-CSF) the incidence of FN was 10% and 94.5% completed the treatment. The incidence of non-hematological adverse events, in 2007 and 2008 combined, was for neuropathy 35%, mucositis 75%, muscle and joint pain 53%, skin rash 25% and fatigue 43% (all grades). *Conclusion*. The introduction of G-CSF was justified because of the high incidence of FN. However, it could not have been predicted after reviewing the published literature. The incidence of non-hematological adverse events had been reported in some, but not all adjuvant taxanes studies. In the future, focus should be more on the side effects, especially when introducing new toxic systemic regimes.

The Danish Breast Cancer Cooperative Group (DBCG) recommended and introduced docetaxel as an integrated part of the adjuvant chemotherapy setting to patients in Denmark after operation for early breast cancer per 1 January 2007. Several meta-analyses [1–5] had showed that taxanes in the adjuvant settings reduced the relative risk of recurrence and death by 20–30% and reduced the absolute risk of recurrence and death after five years by 5% and 3%, respectively [1–4]. Type (paclitaxel or docetaxel), frequency (weekly or every third week), dose and whether to be used sequential or concomitant remain uncertain [5], but the treatment appears to be cost-effective [6,7]. DBCG adapted a French setting (PACS 01 trial) [8] where three cycles of cyclophosphamide and epirubicin (600 mg/m^2, 90 mg/m^2) were followed by three cycles of docetaxel (100 mg/m^2) as it was very close to the previous adjuvant setting used in Denmark, and the side effects seemed acceptable. In the PACS 01 study, no primary prophylaxis with growth factors was used and despite of that, only 11% of the patients experienced febrile neutropenia. Also, the non-hematological side effects were apparently mild, with grade 3 + 4 stomatitis in 6%, nail disorders in 10% and edema in 5%. There were no data regarding neuropathy. The low rate of hematological and non-hematological side effects was in agreement with other published taxan-containing adjuvant studies [9–21].

Twelve months after implementation of the new adjuvant treatment, an unpublished, unsystematic data collection from eight of the 13 treatment

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centers in Denmark (N = 339) showed a high frequency of febrile neutropenia (36%) and severe non-hematological side effects such as stomatitis, neuropathy and pain in muscle and joints. On that background, DBCG decided to give primary prophylaxis with growth factors (G-CSF) concomitant with the first treatment of docetaxel. Furthermore, they also decided to collect all data retrospectively regarding side effects from medical journals across the country.

A retrospective chart review was performed to gather information about the new chemotherapy regime introduced by DBCG regarding dose, complications/toxicity from chemotherapy graded by the NCI Common Toxicity Criteria version 2.0, treatment delay or dose reduction, need for granulocyte colony-stimulating factor and inability to complete chemotherapy course. Furthermore, we tried to elucidate how many of the side effects that could have been foreseen after a meticulous review of already published data.

Method

Study design and registration

All breast cancer in Denmark is registered in the DBCG database, on the basis of data provided from the departments of radiology, pathology, surgery, and oncology. A search in the DBCG database was performed to identify the possible eligible patients, who were treated with adjuvant chemotherapy in the period 1 January 2007 – 1 October 2008 (N = 1353). (Details regarding allocation to treatment with chemotherapy; see www.dbcg.dk.)

Eligible breast cancer patients for this side effects study should be a candidate for adjuvant chemotherapy according to DBCG's guidelines, with epirubicin (90 mg/m$^{2)}$ and cyclophosphamide (600 mg/m^2) (EC) followed by three cycles of docetaxel (100 mg/m^2) (D) given intravenously every third week. They had to have completed the first three cycles of EC and at least have started one cycle with D (N = 1143). Journals had to be available at the 13 departments of oncology. Antiemetic and relevant supportive medications during the treatment period were administrated according to local policy.

We were only able to identify 1143 of 1353 possible patients who fulfilled the criteria for inclusion in this study. The reasons for this discrepancy were, among other factors, that some patients had received preoperative chemotherapy, which was not noted by the DBCG, some patients had refused chemotherapy and others were not offered chemotherapy, either because of high co-morbidity or low performance score.

In the attempt to make the grading and registration of side effects as consistent as possible, all documents (medical journals, nurse documents and toxicity charts) were searched by the same two doctors. Side effects were graded according to the NCIC-CTG version 2.0 criteria. Febrile neutropenia (FN) was defined as leucocytes $<1.5\times109$/l and/or neutrophils <1.0 and fever >38.5°C or repeatedly measured ≥38.0°C, regardless if an infection was documented or not. All patients registered as having a FN had been hospitalized and had received antibiotic.

The results were online registered in the DBCG database.

Treatment modifications in the study period

G-CSF was not routinely used, neither as primary nor as secondary prophylaxis before 1 January 2008. Instead the chemotherapy dose was postponed or reduced according to national guidelines. After 1 January 2008 the DBCG group decided to recommend granulocyte stimulating-factor to all patients as primary prophylaxis when treated with docetaxel in the four to six cycles. One department were not able to accommodate this recommendation at first, but this department only contributed with 51 patients to the study and only three of these patients were treated in 2008 and therefore have no statistic significance. All other departments started the treatment with G-CSF right away which meant that some patients, even though they already received first treatment with docetaxel without G-CSF, received the second treatment with G-CSF. Therefore, for all practical reasons in this study, we define 01 January 2008 as the date where G-CFS where introduced in general as primary prophylaxis in Denmark.

Patient cohorts

The patient material were divided in to cohorts – "2007" and "2008" on the basis of the following criteria:

The 2007 cohort (N = 654) received chemotherapy before primary G-CSF was implemented. Delineation for the 2008 cohort (N = 489) was patients who had received EC + D, with the first D series after 01 February 2008. The purpose of this division was first of all to investigate whether or not the DBCG decision of implementing primary growth factor had an impact on febrile neutropenia and non-hematological side effects.

Results

Patients characteristics

A total of 1143 subjects with operable stage I to II invasive breast cancer were enrolled in this study between January 2007, and October 2008. Disease characteristics are summarized in Table I. There were

no significant difference between the "2007" and "2008" cohorts regarding disease characteristics (data not shown).

Of the 1143 patients included in this study, only 1055 patients received all planned six cycles of chemotherapy (92.4%), see Figure 1. Twenty patients (1.7%) stopped due to what was considered an allergic reaction and 68 patients (5.9%) stopped due to severe hematological and non-hematological side effects. Consequently, almost 8% of the patients did not receive the six pre-planned cycles of chemotherapy. After the introduction of G-CSF, additionally 4% of the patients (90.6% vs. 94.5%) completed the planned treatment.

Non-hematological side effects

Data regarding non-hematological side effects were of inferior quality seen over the entire study period (Table II). In 2007, two thirds of the cases had no information regarding the most common side effects, neither in the medical records nor in the nurses' records. Over time, this improved and in 2008, approximately only half of the patients non-hematological side effects were unknown (data not shown).

Approximately three quarters of the patients had symptoms of stomatitis during the treatment and half of the patients had grade 2 or higher. Around half of the patients suffered from nausea, fatigue and muscle and joint pain, mainly grade 1 and 2, and 7% of the patients had grade 3 and 4 muscle- and joint pain.

Roughly 1/3 of the patients had neuropathy and nail problems (all grades) during the treatment period. One fifth of the patients had neuropathy grade 2 or more after the first dose of docetaxel (data not shown). Diarrhea, skin rash, vomiting and edema where experienced by approximately one fifth of the patients, mainly as grade 1 or 2 side effect. Generally very few patients had a serious (grade 3 or 4) side effect, beside nail problems, muscle and joint pain.

There were no significant differences in side effects among the different subgroups as age, tumor size, numbers of positive lymph node, grade of tumor and receptor status (data not shown).

The impact of growth factor on non-hematological side effects could not be meaningfully analyzed due to the small number of available data.

Hematological side effects

During treatment with EC, 72 patients in 2007 and 2008 together had febrile neutropenia (FN) – 3.8% after the first cycle and less than 2% after the second and third. After the first treatment with docetaxel, 118 patients were hospitalized with FN (10.8%) and after the second and third cycle, only approximately 2% had FN due to either dose reduction or secondary prophylaxis with G-CSF.

Eighty eight patients stopped treatment preplanned because of hematological or non-hematological side effects (see also Figure 1).

The impact of growth factor on FN in the different cohorts – 2007 vs. 2008 - is shown in Table III.

In 2007, before the DBCG recommendation of treatment with primary prophylaxis with G-CSF was made, 27.5% of the planned treatment schedules ended up with FN. Twenty one patients had one or more episodes with FN and the risk of each patient was therefore 25% for being admitted to the hospital with FN. This was reduced after routinely use of G-CSF to 10%. Table III shows that the risk of FN was greatest after the first treatment with docetaxel in 2007 where 15.3% were admitted to the hospital compared to 3.7% in 2008.

Table I. Patients characteristics.

Patients characteristic	Numbers (N) 1143	(%) 100
Age		
<31	20	1.7
31–40	102	8.9
41–50	389	34.0
51–60	501	43.8
61–70	121	10.6
71–80	9	0.8
81–90	1	0.1
Nodal status		
0	433	37.9
1–3	482	42.2
>3	222	19.4
Unknown	6	0.5
Size		
0–20 mm	564	49.3
21–50 mm	528	46.2
>50 mm	42	3.7
Unknown	9	0.8
Malignancy grade		
Grad I	179	15.7
Grad II	473	41.4
Grad III	410	35.9
Non-ductal	81	7.1
ER status		
Negative	368	32.2
Positive	767	67.1
Unknown	8	0.7

Discussion

Because of the inferior quality of the non-hematologal side effects, in this study, seen over the entire study period it is not possible to compare the data with the prospective data from the adjuvant studies. An attempted overview of all of the side effects, though, hampered by the use of different toxicity grading systems, focus on different side effects, reporting

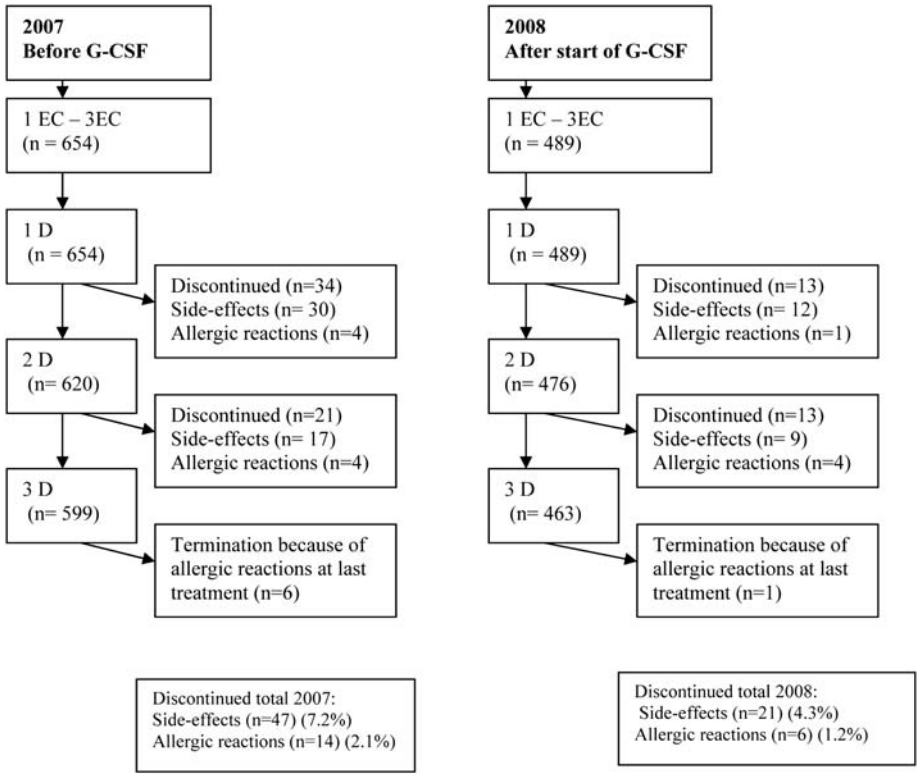

Figure 1. Cause of treatment termination - after cycle 3 and before cycle 6. E=epirubicin, C=cyclophosfamide, D=docetaxel.

toxicity per cycles or per patient, reporting only grade 3 and 4 and even reporting toxicity without defining which toxicity grading system was used in the different studies, is tried illustrated in Tables IV and V.

The hematologic al toxicities data from this study could not have been foreseen from the data published in literature regarding taxane-containing chemotherapy.

Non-hematological side effects

The most striking findings, when looking through the different published studies, were the wide range in reported side effects and the lack of relevant information. In addition, not all studies reported all grades of a side effect. BCIRG [17] and FINHER [20] have most consistently reported the most relevant toxicity and include overall as well as grade 1–2 and 3–4 toxicity. None of the six published paclitaxel studies [9–14] reported incidence or frequency of known side effects such as diarrhea, skin or nail disorders or edema, and docetaxel studies generally reported more side effects then the paclitaxel studies in the adjuvant setting.

One explanation for the variation in reported side effects could be the difference in the type and also

Table II. The maximum incidence of the recorded and non-recorded non-hematological side-effects.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Overall 1–4	Data not available
Stomatitis	175 (15.3%)	230 (20.1%)	606 (53.0%)	14 (1.2%)	0	850 (74.3%)	118 (10.3%)
Diarrhea	213 (18.6%)	130 (11.4%)	71 (6.2%)	14 (1.2%)	2 (0.2%)	217 (19.0%)	713 (62.4%)
Muscles and joint pain	42 (3.7%)	188 (16.4%)	343 (30.0%)	76 (6.6%)	3 (0.3%)	604 (53.3%)	491 (43.0%)
Neuropathy	520 (45.5%)	160 (14.0%)	209 (18.3%)	30 (2.6%)	1 (0.1%)	400 (35.0%)	223 (19.5%)
Skin rash*	194 (17.0%)	151 (13.2%)	121 (10.6%)	17 (1.5%)	—	289 (25.3%)	660 (57.7%)
Nail problems†	128 (11.2%)	212 (18.5%)	107 (9.4%)	—	—	319 (27.9%)	696 (60.9%)
Vomiting	593 (51.9%)	170 (14.9%)	131 (11.5%)	21 (1.8%)	2 (0.2%)	324 (28.3%)	226 (19.8%)
Nausea	305 (26.7%)	350 (30.6%)	295 (25.8%)	26 (2.3%)	3 (0.3%)	674 (59.0%)	164 (14.4%)
Fatigue	42 (3.7%)	272 (23.8%)	195 (17.1%)	25 (2.2%)	2 (0.2%)	494 (43.2%)	607 (53.1%)
Edema‡	166 (14.5%)	121 (10.6%)	64 (5.6%)	4 (0.3%)	—	189 (16.5%)	788 (68.9%)
Others	246 (21.5%)	264 (23.1%)	143 (12.5%)	20 (1.7%)	4 (0.3%)	431 (37.7%)	466 (40.8%)

According to NCI CTC version 2.0 the highest grade of side-effects regarding nails† is grade 2, skin* grade 3 and Edema‡ grade 3.

Table III. Impact of growth factor on FN in the different cohorts – 2007 vs. 2008.

	2007 without G-CSF		2008 with G-CSF	
	Patients n =	Numbers of FN	Patients n =	Numbers of FN
1 EC	654	28 (4.3%)	489	16 (3.2%)
2 EC	654	8 (1.2%)	489	6 (1.2%)
3 EC	654	4 (0.6%)	489	10 (2.0%)
1 D	654	100 (15.3%)	489	18 (3.7%)
2 D	620	19 (3.1%)	476	5 (1.0%)
3 D	599	21 (3.5%)	463	4 (0.8%)

EC, Epirubicin and Cyclophofamide; D, Docetaxel.

in the amount of support medicine used in the different studies. Another explanation is the heterogeneity in the toxicity-reporting scales used – both when comparing studies but also in the single studies, for example the BCIRG stated that they used NCI CTC version 2.0 but reported grade 3 and 4 in their findings regarding nail toxicities, which is not defined in this version.

One of the most dose limiting side effects to docetaxel is neuropathy. Neuropathy were reported within a range of 25% (BCIRG and the concomitant arm of BIG 2-98) to 50% (FINHER and sequential arm of BIG 2-98) overall and from 0% to 18% grade 3 and 4. But the heterogeneity and lack of published data, made an overview of which side effects to be expected very difficult. The reporting of Myalgia in the literature were with an incidence of 23% to 33% overall and 1% to 12% grade 3 and 4. Very few studies stated their findings of artralgia but maybe artralgia were reported as part of myalgia in some of the studies and account for some of the differences. It is well known that G-CSF can result in joint and muscle pain [22,23] and these symptoms are difficult to separate from chemotherapy-induced side effects and could also account for some of the differences.

This study, among the already published studies, also raises the question of what it means to the individual patients to experience several grade 1 or 2 side effects. In daily clinical praxis, the focus is on grade 3 and 4 adverse events, but maybe several grade 1 or 2 side effects have a much higher impact on daily quality of life and are thereby a more meaningful way of expressing the toxicity from a given treatment.

Hematological side effects

Regarding what could have been expected of hematological toxicities, the picture is somewhat different. Again, after attempting an overview of published adjuvant taxane containing treatment (Table V), a large variation in reported febrile neutropenia was found.

As can be seen, three out of 13 studies did not report the criteria by which they define FN (WHO or NCI CTC). In total, five of 12 studies did not report the definition of FN, including PASC01. Looking at the seven studies that did define FN, the numbers of FN appear very scattered even though the same dose of docetaxel and regime (concomitant or sequential) was used.

In the paclitaxel studies the FN varies between 3% and 17% [9,11]. One study did not state the incidence of FN [10]. The variation reflects different doses and schedule of paclitaxel given, but also missing information or different definition of FN, use of G-CSF and prophylactic antibiotic makes the interpretation difficult.

The docetaxel studies reports of FN varying between 5% and 36.9% [12,17]. The US oncology study only reports of 5% FN, which is in contrast to BCIRG 01 at 28.8%. Both studies gave docetaxel in 75 mg/m^2 concomitant with cyclophosphamide and BCIRG also doxorubicin. A difference in definition of FN explains some, but not all. In the US

Table IV. Non-hematological side-effects of adjuvant taxane-containing treatment for early breast cancer, reported in the literature.

Non-hematological side-effect	All grade 1–4%	Grade 1 + 2%	Grade 3 + 4%
Stomatitis literature	34–73.7 [15,17,20]	1–71 [10,15,17,20]	1.0–9 [8,12–21]
Diarrhea literature	35.2 [17]	31.4 [17]	1.5–4 [15,17–19,21]
Myalgia* literature	23.4–33 [14,15,17]	20.6–32 [14,15,17]	0.8–12.4 [9,11,12,14,15,17–19,21]
Neuropathy literature	18–49.7 [10,13,17,20,21]	15–49.5 [10,13,17,20,21]	0–18 [9–14,17–21]
Skin rash literature	26.5–56.5 [17,20]	25.7–55.6 [17,20]	0.3–3.3 [17–21]
Nail problems literature†	18.5–55.9 [17,20]	18.1–55.9 [17,20]	0.4–10.3 [8,17]
Vomiting literature	10.7–44.5 [15,17,20]	10.2–40.2 [15,17,20]	0.5–11.2 [8,12,14,15,17–20]
Edema literature	28–63.2 [15,17,20,21]	27.9–61.6 [15,17,20,21]	0.1–4.8 [8,15,17–21]
Nausea literature‡	0–80.5 [15,17,21]	3–75.4 [10,15,17]	2.0–11.2 [8,12,14,15,17–19]
Allergic reaction	0.6–13.7 [10,13,17,18,20]	0.5–11.7 [10,13,18,20]	0.1–2.0 [10–13,17,18,20,21]
Fatigue literature	78–91.2 [15,17,20]	69.6–83 [15,17,20]	1.1–22 [12,14,15,17–21]

Numbers in brackets refer to the studies reporting the side effect. *Included in some of the reported numbers is also atralgia, †According to NCI CTC version 2.0 the highest grade of side-effect regarding Nails is grade 2, ‡Registered as grade 2 + 3 + 4 in CALBG 9344.

Table V. Hematological side-effects of adjuvant taxane-containing treatment for early breast cancer, reported in the literature and in this study DBCG 07/08.

Study (ref) A. Toxicity grade scale definition B. Definition of FN: Fever and…	N	Treatment regimes	FN
MDACC [9]	265	4 P*(250)+4 FAC(500,50,500)	17%
A. Not stated			
B. Not stated			
CALBG 9344 [10]	1570	4 AC(60/75/90†, 600) + 4P*(175)	Not stated
A. Not stated			
B. Not stated			
NSABP B-28 [11]	1531	4 AC(60,600) + 4P*†(225)	P-cycles alone 3%
A. Not stated			
B. Not stated			
HeCOG [12]	523	4EP‡ (83,187) + 3CMF(840,57,840)	5.9%
A. WHO	540	3E(110) + 3P(250) + 3 CMF	4.6%
B. Not stated			
ECTO [6]	451	4 A(60)P(200) + 4 CMF(600,40,600)	7.7%
A. NCI CTC version 2.0			
B. ANC < 0.5			
GEICAM 9906 [7]	614	4 FEC(600,90,600) + 8P*(100)	5.1%
A. NCI CTC 1.0			
B. Not stated			
US Oncology [8,9]	506	4 DC(75,600)	5%
A. NCI CTC version 1.0			
B. ANC < 0.5			
PACS 01 [14]	996	3 FEC(500,100,500) + 3 D*(100)	11.2%
A. WHO			
B. Not stated			
BCIRG 001[10]	745	6 D*†AC(75,50,500)	28.8%
A. NCI CTC 1.0/2.0)			
B. ANC < 1.0			
ECOG 2197 [11]	1441	4 AD*† (60,60)	17%
A. NCI CTC 2.0			
B. ANC < 1.0			
UK TACT study (CRUK01/001) [12]	2073	4FEC(600,60,600) + 4 D†(100)	7%
A. NCI CTC 2.0			
B. ANC < 1.0			
FINHER [13]	502	3D*(80/100) + 3 EC (600,60,600)	(100) = 36.9% (80) = 14.9%
A. NCI CTC 2.0			
B. ANC < 1.0			
BIG 2-98 [15]	960	3A (75) + 3 D(100) + 3 CMF (100,40,600)	12%
A. NCI CTC 1.0	959	4A(50)D‡ (75) + 3 CMF	16%
B. ANC < 1.0			
DBCG 07/08	654	3 CE(90) + 3 D(100) 2007	25%
A. NCI CTC 2.0	489	3 CE(90) + 3 D‡(100) 2008	10%
B. Leuco < 1.5 and/or ANC < 1.0			

A, doxorubicin; C, cyclophosfamide; E, epirubicin; M, methotrexate; F, fluorouracil; P, paclitaxel; D, docetaxel.
*Secondary G-CSF after 1 FN, †Prophylactics antibiotic used secondary, ‡Primary G-CFS.

oncology study the definition of FN was ANC $< 0.5 \times 10^9$/l and fever and in the BCIRG 01 the definition was ANC $< 1.0 \times 10^9$/l and fever. A higher number of infections in US oncology could account for some of the differences, but the reported incidence of infection was 19% in US ONCOLOGY and 20% for BCIRG 01. But BCIRG 01 also reported FN with the definition of ANC $< 0.5 \times 10^9$/l (data not showed) at 24.7% which is still much higher than US ONCOLOGY. Both studies also used prophylactic administered AB, which therefore cannot give the explanation and US ONCOLOGY did not use G-CSF at all while BCIRG 01 used it secondarily.

The Finnish study FINHER [20] gave docetaxel sequential at 100 mg/m^2 in three series. During their study, FINHER was recommended to reduce their docetaxel dose to 80 mg/m^2 after the finding of FN at 37%. They did not use primary G-CSF or AB. The number of FN declined to 15% after dose reduction. In contrast to this study, PACS 01 which also gave 100 mg/m^2 in three series sequential, found only an incidence of FN of 11% even without the use of primary G-CSF or prophylactic AB. The FINHER

study's definition of FN was 1.0×10^9/l while the PACS 01 study did not report any definition of FN. In the UK TACT study, the patients received docetaxel at 100 mg/m^2 sequential, but only experienced 7% FN (def: ANC $< 1.0 \times 10$ mia/l). This study gave G-CSF depending on the local centers and therefore the exact range of FN is difficult to interpret. Why they in the BIG-98 study, without the use of G-CSF primarily or prophylactic antibiotic, docetaxel 100 mg/m^2 (ANC $< 1.0 \times 10^9$/l) only found 12% with FN is hard to explain.

Our finding of FN at 25% is in concordance with the FINHER and BCIRG 01 study, but not with all the others studies. Therefore, our finding of FN at 25% was not to be expected, and the later decision made by DBCG to use primary prophylactic G-CSF was correct according to ASCO- guidelines, who recommend the use of prophylactic G-CSF in adjuvant chemotherapy when the risk of FN exceeds 20%.

Last but not least, this retrospective study showed that data regarding side effects in standard treatment regimes are registered very poorly, even after introduction of a new toxic treatment modality. In the beginning less than 50% of the patients had their side effect registered and we were therefore "taken by surprise", when severe toxicities were anecdotally reported. What we have learned of this experiment, is that when introducing a new treatment modality, consistent and careful registration of possible side effects is crucial, even when several studies regarding the same regime have been published. A review of reported non-hematological and hematological side effects can only to a very limited degree give an impression of what is to be expected.

Conclusion

Even though several studies regarding effect and side effects of adjuvant taxan-containing chemotherapy have been published in the last decade – results from these studies can not immediately be transferred when a new comparable treatment modality is implemented. Especially the high incidence of FN could not have been predicted, while the findings of the non-hematological side effects could have been expected to a certain extent. Consequently, we would recommend, when a new chemotherapy regime is introduced in the future, that careful registration of all side effects is performed. This accounts of course for both hematological and non-hematological side effects.

Furthermore, as we found the available information in literature very difficult to interpret and sometimes even misleading (different toxicity grading systems focus on different side effects, reporting toxicity per cycles or per patient, reporting only grade 3 and 4 and even reporting toxicity without defining which toxicity grading system, lack of definition of FN and the heterogeneous use of G-CSF and prophylactic AB), we recommend that investigators in the future endeavor to give the most transparent picture to equate the publication of side effects. A possible solution would be to agree on using the same toxicity grading system, use incidence, state all grade 1 to 4 and of course as a minimum, clearly define which definition of FN is used and how the use of G-CSF and prophylactic antibiotic was carried out.

A very important future perspective is also the consequence of getting an understanding of how the patients perceive several grade 1 side effects. Is this as serious as one grade 3 or 4 side effect? Should these findings lead to a dose reduction similar to grade 3 or 4 side effects? More work is warranted on this area.

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