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CLINICAL TRIAL

Concomitant docetaxel plus gemcitabine versus sequential docetaxel followed by gemcitabine in anthracycline-pretreated metastatic or locally recurrent inoperable breast cancer patients: a prospective multicentre trial of the Central European Cooperative Oncology Group (CECOG)

Antoaneta Tomova · Rupert Bartsch · Thomas Brodowicz · Valentina Tzekova · Constanta Timcheva · Christoph Wiltschke · Dany Abi Gerges · Jan Pawlega · Stanislav Spanik · Moshe Inbar · Christoph C. Zielinski

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Abstract Docetaxel (D) plus gemcitabine (G) is an active combination in anthracycline pre-treated breast cancer. Impact of sequential administration of these drugs is unclear. This trial aimed to compare concomitant DG with sequential D → G. Patients were randomised to eight cycles of gemcitabine 1,000 mg/m^2 on days 1 + 8 plus docetaxel 75 mg/m^2 on day 8, or 4 cycles of docetaxel 100 mg/m^2 on day 1, followed by four cycles of gemcitabine 1,250 mg/m^2 on days 1 + 8, in a 21-day schedule. Time to progression (TTP) was defined as primary endpoint; secondary endpoints were overall response rate (ORR), response duration (RD), overall survival (OS) and toxicity. Due to poor recruitment, the trial was terminated after 100 of a pre-planned 430 patients. Patient characteristics were well balanced. No significant difference was observed in terms of TTP, ORR, RD and OS. Grade 3/4 adverse events encompassed leucopoenia (29 vs. 68%, $P < 0.001$), neutropoenia (49 vs. 83%, $P < 0.001$) and febrile neutropoenia (4 vs. 9%, n.s.), all favouring D → G. No difference in efficacy was observed between concomitant and sequential treatment. D → G produced significantly more episodes of haematological toxicity due to the administration of docetaxel at 100 mg/m^2 without GCSF-support.

Keywords Metastatic breast cancer · Chemotherapy · Sequential versus concomitant · Gemcitabine · Docetaxel

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Introduction

Breast cancer is one of the most prevalent cancers in the world and causes approximately half a million deaths per year worldwide [1]. In the U.S. alone, nearly 200,000 women are affected per year [2].

While the clinical course is highly variable, up to one-third of the patients with stage I and II disease are expected to experience recurrence [3]. Metastatic breast cancer remains an incurable disease. Thus, palliation of symptoms and, where possible, prolongation of survival are major therapeutic goals [4]. Combination chemotherapy administered as front-line treatment for metastatic disease usually results in 35 to 75% objective responses. However, complete responses are rare and the average duration of response is 8 months

only [5]. Corresponding numbers are even lower in the second-line setting [6, 7].

Currently, taxanes and anthracyclines are among the most active substances available [8]. A meta-analysis conducted by Fosatti et al. suggested a small yet significant survival benefit for polychemotherapy over sequential single-agent treatment [9]. Therefore, combination chemotherapy was regarded standard of care in many European countries.

Upon progression on anthracyclines, taxanes are among the most widely utilised agents. Docetaxel is a semisynthetic taxane; it acts through disruption of mitosis, promotes microtubule assembly, and suppresses microtubule depolymerisation. As first-line monotherapy for metastatic breast cancer, docetaxel produces response rates in excess of 50% [10]. Even for patients who relapsed or progressed on prior anthracyclines, response rates were rather high (41–48%) [11, 12]. In a study conducted by O'Shaughnessy et al. the combination of capecitabine and docetaxel was found superior over docetaxel alone in terms of overall survival [13]. Regimens using gemcitabine and taxanes yielded similar efficacy, yet less non-haematological side effects were observed, rendering this an attractive combination [13–15].

Gemcitabine (2′,2′-difluorodeoxycytidine) is a fluorine-substituted cytarabine (Ara-C) analogue with proven activity in a number of human cancers [16]; Ara-C, while one of the most effective drugs for the treatment of certain blood malignancies [17], has limited activity in solid tumours [18]. In contrast to Ara-C, membrane permeability and enzyme affinity of gemcitabine is enhanced, as well as duration of intracellular retention [18, 19]. Of note is a suspected in vivo synergism between docetaxel and gemcitabine, which renders this combination especially attractive [20].

As no formal comparison of gemcitabine and docetaxel combination chemotherapy with the same agents in a pre-planned sequential design has been conducted, the Central European Cooperative Oncology Group (CECOG) initiated this prospective, randomised trial. A benefit for the sequence of docetaxel followed by gemcitabine was assumed, as sequential therapy may allow delivery of a single drug in a rapid repetitive fashion [21].

Patients and methods

Concomitant versus sequential docetaxel and gemcitabine was planned as a randomised, open label and phase III trial designed to compare the efficacy and tolerability of a concomitant versus pre-planned sequential approach in patients with anthracycline pre-treated metastatic breast cancer. The study was conducted by the Central European Cooperative Oncology Group (CECOG). A total number of 14 centres from Europe, Israel and Lebanon recruited patients to this study. The trial was performed in accordance with the ethical regulations of the participating centres and has been approved by the appropriate local ethics committees prior to its initiation.

Patients

A total number of 100 patients (from a pre-planned 430) were included from September 2002 until March 2006 and followed prospectively. Ninety-nine patients are currently eligible for evaluation for toxicity, and 98 for response. Data were analysed as of December 2007.

All patients had histologically confirmed breast cancer with evidence of unresectable, locally recurrent or metastatic disease. Criteria for inclusion were as follows: Females, 18 to 75 years of age, Karnofsky performance score $\geq$70 and life expectancy of >3 months with unresectable, locally recurrent or metastatic breast cancer and written informed consent. Prior treatment with one anthracycline containing regimen for either early or metastatic disease was mandatory. Endocrine therapy and trastuzumab were allowed until the day of randomisation. Adequate bone marrow reserve (white blood cell [WBC] count $>3.0 \times 10^9$/L, neutrophil count [ANC] $\geq 1.5 \times 10^9$/L, platelets $> 100 \times 10^9$/L, haemoglobin > 10 g/L), as well as adequate liver and renal function, were required (bilirubin $\leq$1.5 times the upper limit of normal [ULN]); alanine transaminase [ALT] and aspartate transaminase [AST] $\leq$2 times the ULN; creatinine $\leq$1.5 times the ULN]). In women of childbearing potential use of an approved contraceptive method during and for 3 months after trial was mandatory.

Major exclusion criteria included: Two or more prior chemotherapeutic regimens for metastatic disease; concurrent irradiation, chemotherapy, hormonal therapy or immunotherapy; previous chemotherapy containing gemcitabine or taxanes; known or suspected brain metastases requiring steroids or irradiation; pregnancy or breast-feeding; history of second primary malignancy (except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin); bone marrow transplantation or stem cell infusion following high-dose chemotherapy; use of any other investigational agent within 4 weeks prior to study enrolment; symptomatic peripheral neuropathy >grade 2 according to CTC.

For baseline staging evaluations, CT-scans of the chest and the abdomen, bone scan, mammography and gynaecologic examination were mandatory, with further work-up if indicated. No central radiological review was conducted.

Trial treatments

The primary objective of this study was to compare time to disease progression (TTP) between patients randomised to

docetaxel plus gemcitabine and patients treated with the sequence of docetaxel followed by gemcitabine. Secondary study endpoints were overall response rate (ORR; CR + PR), duration of response, overall survival (OS) and toxicity.

Patients were randomly assigned to either of two treatment arms (Fig. 1). Arm A (concomitant arm): gemcitabine plus docetaxel administered intravenously for a total of eight cycles. Arm B (sequential arm): four cycles of docetaxel followed by four cycles of gemcitabine.

Patients randomised to arm B who discontinued docetaxel early due to progression or unacceptable toxicity were switched to gemcitabine monotherapy. All patients receiving docetaxel had steroid pre-medication according to local standards.

Treatment in both arms continued until eight cycles were administered. Patients remained on study until objective disease progression was documented or other events that required discontinuation occurred. At this time-point, patients were taken off study and further therapy was initiated at the discretion of the treating physician.

Response evaluation

Re-evaluation of patients' tumour status was performed in both arms every other cycle and in two-month intervals thereafter. Response was assessed using RECIST criteria.

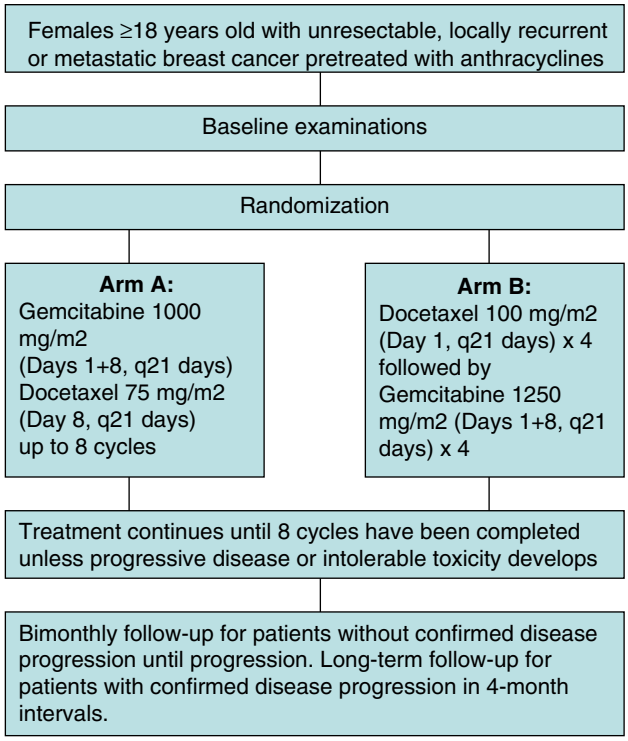

Fig. 1 Trial design. **Arm A** Concomitant treatment with eight cycles of docetaxel and gemcitabine. **Arm B** Sequential treatment with four cycles docetaxel followed by four cycles gemcitabine

Complete response (CR) was defined as the disappearance of all measurable lesions for a minimum of eight weeks. Partial response (PR) was defined as 30% or more reduction in sum of the longest diameters of target lesions, no increase of lesion size and no new lesions. Stable disease (SD) was defined as less than 30% decrease and less than 20% increase without the appearance of new lesions. Progressive disease (PD) was defined as at least a 20% increase in tumour size or the appearance of new lesions.

Safety

Adverse events (AEs) were recorded throughout the treatment period and were graded according to CTC according to treatment received.

Dose reduction

Doses were reduced by one dose level (as defined per protocol) in case of the following haematological toxicities: ANC $< 0.5 \times 10^9$/L for more than 5 days; ANC $< 0.1 \times 10^9$/L for more than 3 days; febrile neutropoenia; platelets $< 25 \times 10^9$/L for three or more days. In addition, doses were reduced by one dose level if the next cycle was delayed for more than one week due to toxicity. In case of grade 3 non-haematological toxicity, a dose reduction by one level was recommended.

Statistical analysis

Randomisation was stratified according to the following factors: Karnofsky Performance Status (70–80 vs. 90–100); presence of visceral metastases (yes vs. no); anthracycline pre-treatment in the adjuvant versus metastatic setting; disease progression following prior adjuvant chemotherapy (≤6 months vs. >6 months); investigational centre (by centre).

All patients who received at least 1 dose of gemcitabine or docetaxel were available for safety analysis. All patients with a minimum of one response assessment were also evaluable for efficacy. Patients who dropped out of protocol prior to cycle two and did not have response assessment were excluded.

TTP was defined as interval from first cycle until documented disease progression or death of any cause while on treatment, and estimated using the Kaplan–Meier product-limit method. In order to test the differences between TTP curves, the log-rank test was used. The analysis of AEs was performed using a two-sided Fisher's exact test. P values less than 0.05 were considered to indicate statistical significance. Data were analysed as of December 2007. All statistics were calculated using statistical package for the social sciences (SPSS®) 12.0 software (SPSS Inc., Chicago, IL, USA).

Sample size

Initially, the inclusion of 430 patients was planned. Using a 5% significance level, this sample size would have provided an approximately 80% chance of finding a significant difference in time to progression of 7–9.1 months. This probability assumes a hazard ratio of 0.75 in favour of the sequential arm with 10% censoring (i.e., approximately 385 progression-free survival events observed). This hazard ratio corresponds approximately to a 33% increase in time to documented progression of disease under the exponential distribution assumption. Given the early termination of the study due to poor accrual, the trial is underpowered to detect the assumed difference in terms of TTP.

Results

Patient characteristics

A total of 100 of 430 pre-planned women were recruited and randomly assigned to concomitant docetaxel plus gemcitabine (DG) ($n = 46$) or sequential docetaxel followed by gemcitabine (D → G) ($n = 54$). The trial was terminated early in March 2006 due to slow recruitment. As of December 2007, 99 patients were evaluable for safety (99%) and 98 for efficacy (98%). Approximately one quarter of patients completed treatment in both arms (26% DG versus 28% D → G; n.s.). Main reasons for treatment discontinuation included: Disease progression (44% vs. 56%), adverse events (6.5% vs. 5.6%) and patient wish (15% vs. 5.6%). Baseline characteristics (safety population) are outlined in Table 1. Overall, the groups were well balanced, except that the sequential cohort had a higher number of patients with KPS ≥ 90 (60% vs. 38%; $P = 0.015$).

Median age was 52 and 55 years (n.s.), 70% of patients in both groups were diagnosed with grade 3 tumours, half had oestrogen-receptor positive disease, and around 20% were Her2-positive (23% vs. 17%; n.s.), none of whom had received prior trastuzumab. Median follow-up for the concomitant group was 20.3 months (95% CI 15.4–32.0) and 19.3 months (95% CI 14.2–22.6) in the sequential group, respectively.

Efficacy

TTP was defined as primary study end point. At the time of analysis, 73% of the concomitant and 76% of the sequential group had experienced a pre-defined progression event. The median time to progression was 7 months in the DG

Table 1 Patient characteristics (safety population)

Characteristics	DG	D → G
Randomly assigned	46 patients	53 patients
Karnofsky performance score		
80	27%	11%
90	36%	28%
100	38%	60%
Age (years) mean (SD)	52.3 year (9.6)	54.9 (9.5)
Histological diagnosis		
Invasive ductal carcinoma	70%	74%
Invasive lobular carcinoma	13%	9.4%
Other	17%	17%
Pathological grading		
G1	-	2%
G2	37%	37%
G3	30%	35%
G4	0%	5.9%
GX	33%	20%
Oestrogen receptor		
Positive	39%	34%
Negative	52%	55%
Unknown	8.7%	11%
Progesterone receptor		
Positive	41%	42%
Negative	50%	47%
Unknown	8.7%	11%
Her2 status (IHC/FISH*)		
Negative	77%	83%
Positive	23%	17%
Stage of diasease at time of diagnosis		
Stage I	2.2%	5.7%
Stage II	61%	53%
Stage III	28%	28%
Stage IV	8.7%	13%
Summary of prior anticancer therapy		
Prior adjuvant radiotherapy	44%	42%
Prior chemotherapy	100%	100%
Prior hormonal or immunotherapy	65%	70%
Prior surgery	85%	94%
Time since initial diagnosis (years)		
Mean (SD)	4 year (3.4)	3.9 (3.1)
Localisation of metastatic sites		
Lung	44%	47%
Liver	52%	42%
Bones	26%	28%

* *IHC* immunohistochemistry, Herceptest® (Dako A/S, Glostrup, Denmark); FISH: dual colour fluorescent in situ hybridisation (PathVision® HER2 DNA probe kit, Vysis Inc., Downers Grove, IL, USA)

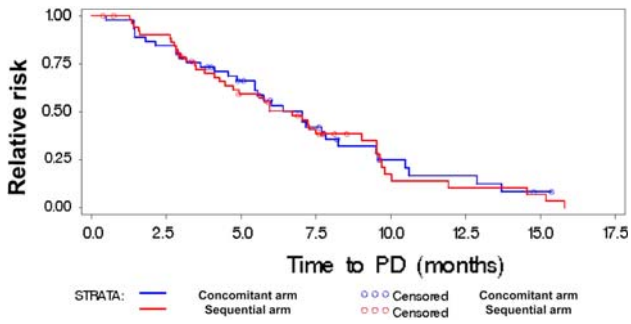

Fig. 2 Time to progression (TTP; months)

arm (95% CI 5.5–8.2) as compared to 6.7 months (95% CI 4.7–9.0) for patients on D → G (Fig. 2). The log-rank test revealed no significant difference ($P = 0.8$).

Overall, 14 patients in the concomitant arm (31%; 95% CI 18.2–46.6) and 15 patients in the sequential arm (28%; 95% CI 16.8–42.3) had a documented response (n.s.). A further 19 patients on DG (42%) and 18 patients on D → G (34%) experienced disease stabilisation for a minimum of 8 weeks (Table 2).

The median duration of response, as measured from the date of random assignment, was 5.4 months (95% CI 3.4–6.8) in the concomitant and 7.8 months (95% CI 6.3–11.1) in the sequential group, respectively ($P = 0.147$).

Median overall survival was 15.5 months (95% CI 13.7–19.8) in the DG group as compared to 15.9 months (95% CI 11.3–22.2) in the D → G group (Fig. 3) ($P = 0.346$).

Table 2 Response rates (n = 98)

	Number	Response*				
		CR	PR	SD	PD	NA
DG	$n = 45$	0 (0%)	14 (31%)	19 (42%)	8 (18%)	4 (8.9%)
D → G	$n = 53$	1 (1.9%)	14 (26%)	18 (34%)	11(21%)	9 (17%)

* *CR* complete response; *PR* partial response; *SD* stable disease; *PD* progressive disease; *NA* not assessable

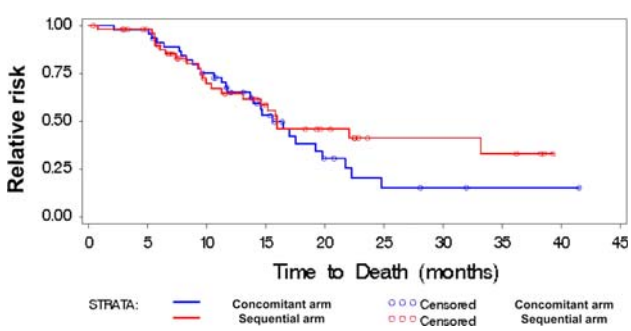

Fig. 3 Overall survival (OS; months)

Tolerability

Patients eligible for assessment of toxicity ($n = 99$) included 46 patients in the concomitant and 53 in the sequential arm, all of whom received at least on dose of study drug. In the combination arm, the median delivered dose of docetaxel during the course of study was 100%, and the corresponding value for gemcitabine was 89%. In the sequential arm, the overall median delivered dose was 94% for docetaxel and 91% for gemcitabine. Therefore, the median-delivered relative dose of docetaxel was significantly lower in the sequential arm ($P = 0.001$). A dose reduction was performed in 15% of patients in the concomitant arm and 30% receiving sequential therapy ($P = 0.078$; n.s.). Dose delays were necessary in 46% of patients receiving DG, and 23% on D → G ($P = 0.015$).

The overall incidence of treatment-related adverse events was similar in both arms (80% DG vs. 81% D → G; n.s.); also, no significant difference was found in the total number of serious adverse events (17 vs. 17%), however, two serious adverse events with fatal outcome were recorded in the concomitant treatment arm (one case of congestive heart failure, one case of enterocolitis).

Incidence of non-haematological toxicity was comparable, although a slightly higher incidence of non-neutropoenic fever as well as peripheral oedema was reported in patients receiving DG (13 vs. 1.9%, $P = 0.035$; 10.9 vs. 1.9%, $P = 0.066$; n.s.). A significantly larger proportion of patients in the D → G group experienced severe leucopoenia and neutropoenia as compared to the concomitant arm (grade 3/4 leucopoenia: 68 vs. 29%; $P < 0.001$; grade 3/4 neutropoenia 83 vs. 49%; $P < 0.001$). As outlined above, this difference did not translate into a higher incidence of serious adverse events. No significant difference was observed in terms of thrombocytopoenia, however, a significantly higher number of patients in the DG group experienced anaemia >grade 1 ($P = 0.003$). Haematological side effects were the main reason for dose delays and dose reductions on both arms. Toxicities are summarised in Table 3.

Discussion

Although terminated prematurely, this prospective randomised trial demonstrates that the combination of docetaxel and gemcitabine is feasible and relatively safe both as concomitant treatment and in a pre-planned sequential design. The reason for the poor accrual is not entirely clear, but possibly investigators' focus has shifted towards studies incorporating targeted agents. No difference was observed in terms of time to disease progression, overall response rate, duration of response and overall survival. However, sequential administration of docetaxel and gemcitabine was

Table 3 Toxicity ($n = 99$)

Toxicity	CTC Grade	DG (%)	D → G (%)
Haematological			
Haemoglobin (Hb) $P = 0.003$	Grade 1	47	60
	Grade 2	49	21
	Grade 3	2.2	3.8
	Grade 4	-	-
Leucocytes (total WBC) $P < 0.001$	Grade 1	13	7.5
	Grade 2	36	19
	Grade 3	20	42
	Grade 4	8.9	26
Neutrophiles (ANC) $P < 0.001$	Grade 1	13	3.8
	Grade 2	16	7.5
	Grade 3	29	17
	Grade 4	20	66
Platelets	Grade 1	29	23
	Grade 2	-	-
	Grade 3	4.4	-
	Grade 4	-	-
Fever (neutropoenic) n.s.	Grade 1	-	-
	Grade 2	-	-
	Grade 3	4.3	5.7
	Grade 4	-	3.8
Non-Haematological			
Allergic reactions n.s.	Grade 1	-	-
	Grade 2	2.2	-
	Grade 3		-
	Grade 4		-
Oedema $P = 0.066$	Grade 1	-	-
	Grade 2	8.7	-
	Grade 3	-	1.9
	Grade 4	2.2	-
Thrombosis/Embolism n.s.	Grade 1	-	-
	Grade 2	-	-
	Grade 3	2.2	-
	Grade 4	-	-
Fatigue n.s.	Grade 1	-	-
	Grade 2	-	-
	Grade 3	4.3	3.8
	Grade 4	-	-
Fever (w/o neutropoenia) $P = 0.035$	Grade 1	6.5	-
	Grade 2	6.5	-
	Grade 3	-	1.9
	Grade 4	-	-
Nail changes n.s.	Grade 1	-	-
	Grade 2	-	-
	Grade 3	2.2	-
	Grade 4	-	-
Diarrhoea n.s.	Grade 1	-	1.9
	Grade 2	6.5	9.4
	Grade 3	4.3	-
	Grade 4	-	-
Nausea n.s.	Grade 1	-	1.9
	Grade 2	-	-
	Grade 3	2.2	-
	Grade 4	-	-
Vomiting n.s.	Grade 1	-	-
	Grade 2	2.2	-
	Grade 3	2.2	-
	Grade 4	-	-
Neuropathy-motor n.s.	Grade 1	-	-
	Grade 2	-	1.9
	Grade 3	-	-
	Grade 4	-	-
Neuropathy-sensory n. s.	Grade 1	-	1.9
	Grade 2	2.2	-
	Grade 3	-	-
	Grade 4	-	-
Myalgia n.s.	Grade 1	2.2	-
	Grade 2	-	1.9
	Grade 3	-	-
	Grade 4	-	-

associated with a significantly higher incidence of grade 3/4 neutropoenia. As only 98 of a planned 430 patients are available for efficacy analysis, those data need to be interpreted with caution.

Concomitant DG in our trial yielded a TTP of median 7.0 months. Those results compare well with data from a phase II trial of weekly DG as first-line chemotherapy [15]. Mavroudis et al. observed similar results: They reported 8.0 months median TTP in anthracycline-pretreated patients; response rates on the other hand were higher when compared to our study (44% vs. 31%). This might be explained by the higher dose of docetaxel (100 mg/m^2), as compared to 75 mg/m^2 in the concomitant arm of our trial [22]. In a phase III trial comparing DG to docetaxel and capecitabine in anthracycline-pretreated patients, docetaxel was administered in a dose of 75 mg/m^2. Similar to our results, this group observed a response rate of 27% [14].

Up to this day, the optimal treatment approach in metastatic breast cancer, with anti-tumour agents given sequentially or in combination, remains controversial. Interestingly, there is some agreement that neither strategy will fit all patients [23]. Following the publication of a

meta-analysis by Fossati et al. [9], it was commonly accepted that polychemotherapy may be associated with higher toxicity, while a small yet significant benefit in terms of overall survival was gained (HR 0.82). This publication, however, suffered from a number of limitations. Most of the trials included were small and many featured older regimens. Furthermore, most studies conducted in this field did compare polychemotherapy to single-agent treatment, although it would be more pertinent to compare polychemotherapy to a pre-planned sequential design utilising the same drugs.

In a randomised phase III study comparing the combination of docetaxel and capecitabine with docetaxel alone, polychemotherapy was associated with significantly longer overall survival [13]. Still, this study did not use a pre-planned sequential design as comparator. Among the 164 patients who received any post-study chemotherapy, only 27% were subsequently treated with capecitabine. Therefore, it must be stated that a survival advantage of the combination over a truly sequential therapy was not demonstrated [23].

The rational of our study was to compare concomitant administration of DG with the same agents in a pre-planned sequential manner. Since its initiation, a number of other studies with similar design have reported, and our data must be discussed in the light of their results. In a phase III trial conducted by Sledge et al. over 700 chemotherapy naive patients were randomised to one of three treatment arms [24]. Subjects received doxorubicin followed by paclitaxel upon disease progression, paclitaxel followed by doxorubicin upon progression or a combination of those agents. Polychemotherapy was associated with superior response rates and time to treatment failure, but failed to demonstrate a survival benefit. In another trial, around 200 patients were randomised to docetaxel, followed by doxorubicin upon progression or after a maximum of four cycles, or a combination regimen of docetaxel plus doxorubicin. This trial therefore used a design similar to our study. While response rate was superior in the combination arm, this did not translate into improved progression-free or overall survival [25]. Our results are apparently well in line with those studies, although as mentioned, our data suffer from impaired statistical power.

Data regarding toxicity are comparable to other trials utilising docetaxel either as single agent [26] or in combination with gemcitabine [27, 28]. Naturally, a lower rate of leucopoenia was observed in a study of weekly DG [15], as well as in a trial of DG with GCSF-support [22]. The only major difference in terms of toxicity between the two arms in our trial was an increased rate of grade 3/4 leucopoenia and neutropoenia in the sequential arm. Although this might contradict conventional perception of better tolerability of single-agent treatment, the same most probably results from the use of full-dose docetaxel (100 mg/m^2) without GCSF-support.

In conclusion, this trial was not able to detect an anticipated difference associated with polychemotherapy versus sequential single-agent treatment in terms of time to disease progression. Premature termination after the inclusion of only 100 of a pre-planned 430 patients reduces the validity of our data, and the trial has not enough power to detect small differences in efficacy. As for the design of this study, future trials should target specific aspects of treatment individualisation.

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