Journal of Cancer Research & Therapy

Galdy S et al., J Cancer Res Ther 2014, 2(2):40-47
http://dx.doi.org/10.14312/2052-4994.2014-6

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Original research

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Adjuvant concurrent docetaxel, epirubicin and cyclophosphamide chemotherapy in breast cancer: The TEC regimen. A retrospective analysis

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Abstract

Background: The use of taxanes and anthracyclines in the adjuvant treatment of primary breast cancer is well established, with benefit in both disease free survival (DFS) and overall survival (OS). Several studies demonstrated that the addition of taxanes to anthracycline-based chemotherapy improves the outcome in either concurrent or sequential schedule. Nowadays, the TAC regimen (docetaxel, doxorubicin and cyclophosphamide) is a standard treatment in both node-positive and high-risk node-negative early breast cancer. Doxorubicin and epirubicin are equivalent, but at similar doses epirubicin appears to have a better side effects profile than doxorubicin in terms of myelosuppression and cardiotoxicity. We conducted a retrospective study to establish the role of TEC (epirubicin) regimen in adjuvant setting. *Methods:* Pre- or post-menopausal women, with stage I-III breast cancer, PS ECOG 0-2 and normal left ventricular ejection fraction, were eligible. TEC chemotherapy at median doses of docetaxel 75 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 500 mg/m^2 was administered IV on day 1 every three weeks for 6 cycles. The primary endpoint was toxicity; secondary endpoints were DFS and OS. *Results:* Thirty-three consecutive female patients were retrospectively enrolled. The median age was 57 years old. Eighty eight percentage of patients completed the treatment plan. In 21.2% of cases a dose reduction was performed and these patients needed a chemotherapy interval prolongation. The main side effects were neutropenia G3-4 (21.2%; 95% CI, 9.8-37.5), allergic reaction G3 to docetaxel (6.1%; 95% CI, 1.0-18.6) and febrile neutropenia (3.0%; 95% CI, 0.1-14.0), while cardiotoxicity was absent (95% CI, 0-8.7%). Globally, the percentage of any other severe side effect was very low and no one toxic death was seen. The 3-year DFS and OS were 89.9% (95% CI, 79.0-100) and 93.8% (95% CI, 85.6-100), respectively. *Conclusions:* As compared to TAC treatment, TEC regimen with epirubicin 60 mg/m^2 is feasible and well tolerated adjuvant chemotherapy in breast cancer, with acceptable and manageable toxicity.

Keywords: docetaxel; epirubicin; cyclophosphamide; adjuvant; breast cancer

Introduction

In the United States, breast cancer is the most common female malignancy, excluding cancers of the skin, and it is the second leading cause of cancer death in women, after lung cancer [1]. In Italy, the estimated incidence and mortality rates for breast cancer are 114 and 24 per 100,000 inhabitants per year, respectively [2]. However, the breast cancer early diagnosis, performed by screening programs, and the adjuvant combined treatments may improve the disease free survival (DFS) and overall survival (OS).

Adjuvant chemotherapy represents a standard of care for this pathology and in the last 30-40 years we have

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Received 3 November 2013 *Revised* 6 January 2014 *Accepted* 14 January 2014 *Published* 20 January 2014

Citation: Galdy S, Zenoni D, Galmozzi A, Mauri CM, Cazzaniga S (2014) Adjuvant concurrent docetaxel, epirubicin and cyclophosphamide chemotherapy in breast cancer: The TEC regimen. A retrospective analysis. J Cancer Res Ther 2:40-47. doi:10.14312/2052-4994.2014-6

assisted to some significant changes. The addition of anthracyclines and taxanes to adjuvant chemotherapy, in different combinations (concurrent or sequential), had a big impact on the natural history of the breast cancer [3-5].

Two randomized phase III studies investigated the use of a three-drug combination known as TAC chemotherapy (docetaxel, doxorubicin and cyclophosphamide) versus the FAC chemotherapy (5fluouracil, doxorubicin and cyclophosphamide) in the adjuvant setting of early breast cancer, either node-positive or node-negative at high-risk of recurrence, with benefit in both DFS and OS [6, 7]. TAC regimen improves the outcome; on the other hand it also increases the risk of toxicity.

In view of the high and frequent toxicity associated to TAC regimen, we carried out a retrospective study to explore the hypothesis that TEC regimen substituting doxorubicin with epirubicin may improve tolerability.

Patients and methods

Eligibility

Pre- or post-menopausal women with histologically confirmed breast cancer, no evidence of distant metastases, aged ≥18 years, Eastern Cooperative Oncology Group scale (ECOG) performance status (PS) ≤2, normal left ventricular ejection fraction (LVEF ≥51%) as assessed by echocardiogram, adequate hematological, renal and hepatic function, were eligible for the study; no previous chemotherapy nor radiotherapy was permitted. Cardiac toxicity was defined as LVEF decrease ≥20% points from baseline; LVEF was measured at baseline and at the end of chemotherapy, thereafter every 6 months. For all patients, the following variables were recorded: sex, age, performance status according to ECOG scale, type of tumor (CDI or CLI), stage of disease, grading, hormone receptor status and HER-2 status by IHC and/or FISH test. Patients and disease characteristics are shown in Table 1.

Table 1 Patients and disease characteristics

		No. of Patients (n=33)	*% Patients*
Age			
	Median	57	
	Range	47-73	
Gender			
	Female	33	100
ECOG Performance status			
	0	32	97
	2	1	3
Histology			
	Ductal	31	94
	Lobular	2	6
Stage: AJCC, 7th Edition			
	I	1	3
	IIA	6	18.2
	IIB	14	42.4
	IIIA	7	21.2
	IIIB	2	6.1
	IIIC	3	9.1
Hormone receptor statusα			
	ER positive/PR positive	29	88
	ER negative/PR negative	4	12
HER-2 statusβ			
	HER-2: IHC 3+δ	14	42.4
	HER-2: IHC 2+/FISH negative	11	33.3
	HER-2: IHC 1+	8	24.3

Abbreviations: αHormone receptor status: ER: Estrogen receptor; PR: Progesterone receptor; βHER-2 status: Human epidermal growth factor receptor 2; IHC: Immunhistochemistry; FISH: Fluorescence in situ hybridation; δAll 14 HER2-positive patients, still alive at the end of adjuvant chemotherapy, received Trastuzumab 375 mg/m^2 on day 1 every 3 weeks for a planned program of 18 cycles.

Treatment schedule

Premedication with antiemetics and steroids was planned systematically. Treatment schedule and dose reduction protocol were chosen at discretion of investigator. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was proposed to overall population for a potential risk of febrile neutropenia ≥20%. Dexrazoxane prophylaxis was chosen at discretion of the attending physician. Each patient received the TEC regimen at these median starting doses: Docetaxel (T) 75 mg/m^2, Epirubicin (E) 60 mg/m^2 and Cyclophosphamide (C) 500 mg/m^2 IV on day 1 every 3 weeks for six cycles. The mean and median starting doses of chemotherapy are shown in Table 2 and the TEC treatment plan (final doses) are shown in Table 3. HER-2-positive patients, at the end of adjuvant chemotherapy, would have been treated with Trastuzumab 375 mg/m^2 on day 1 every 3 weeks for a planned program of 18 cycles.

Table 2 TEC treatment plan (starting doses)

	Mean starting doses	*Standard Deviation (SD)*	*Median doses*	*Range*
Docetaxel (T)	74.7 mg/m^2	1	75 mg/m^2	70-75
Epirubicin (E)	61.2 mg/m^2	11.1	60 mg/m^2	50-90
Cyclophosphamide (C)	489.8 mg/m^2	38.7	500 mg/m^2	313-500

Table 3 TEC treatment plan (final doses)

	Mean final doses	*Standard Deviation (SD)*	*Median doses*	*Range*
Docetaxel (T)	71.5 mg/m^2	6.2	75 mg/m^2	56-75
Epirubicin (E)	58.7 mg/m^2	12.3	60 mg/m^2	38-90
Cyclophosphamide (C)	470.8 mg/m^2	51.6	500 mg/m^2	313-500

Statistical analysis

The primary endpoint was the incidence of grade 3-4 toxicity; hematological and non-hematological toxicity was recorded according to NCI Common Toxicity Criteria, version 3.0 [8]. When planning this retrospective study, we estimated that at least 33 patients were needed in order to detect incidence rates of 25% or lower with a maximum acceptable error of 15%. Patients' toxicities were reported as absolute numbers and percentages, together with their 95% confidence intervals (CI). Continuous variables were described by using median and range or by mean and standard deviation (SD). Each patient was analyzed for the frequency of drug toxicity, dose reduction or delay.

The secondary endpoints were disease free survival (DFS) and overall survival (OS). Disease free survival was defined as the interval from the start date of chemotherapy to the date of first loco-regional or metastatic relapse; diagnosis of a secondary cancer (excluding no-melanoma cancer); last follow up visit if disease had not progressed. Overall survival was defined as the interval between the beginning of treatment and death for any cause or last follow up visit. For the purpose of our analysis DFS and OS were limited to a three years follow up period. Survival probabilities were calculated according to Kaplan-Meier product limit estimator and were presented together with their 95% (CI) estimates [9]. Statistical analysis was carried out by using SPSS software, version 17.0 (SPSS Inc, Chicago, IL).

Results

Toxicity

The data of 33 consecutive female patients with early and/or operable breast cancer, underwent adjuvant TEC chemotherapy between February 2008 and June 2010 at the Division of Oncology of the Hospital "Bolognini" of Seriate (Bergamo, Italy), were retrospectively collected and monitored until June 2012. The median age was 57 years (range 47-73). All patients received at least one cycle of chemotherapy and were evaluable for toxicity. A total of 186 courses were given, with a median of 6 cycles (range, 2-6) per patient. The 87.9% of patients completed the treatment program. Just four (12.1%) chemotherapies were prematurely interrupted: two (6.1%) for adverse reaction to docetaxel, one (3.0%) for relapse disease and one (3.0%) in accordance to the will of the patient. In 7/33 (21.2%) of cases a dose reduction was performed, with an overall mean dose-chemotherapy reduction of 4.1% (Table 4). These patients needed also a

Table 4 Mean dose-chemotherapy reduction

	Mean dose reduction	*Standard Deviation (SD)*
Docetaxel (T)	4.3%	8.0
Epirubicin (E)	4.2%	8.0
Cyclophosphamide (C)	3.8%	7.6
All	4.1%	7.8

chemotherapy interval prolongation, with a mean delay of 10.1 days (5 patients for neutropenia G3-4, 1 patient for febrile neutropenia and 1 patient for diarrhea G3-4).

The vast majority of patients (94%) received a primary G-CSF prophylaxis (pegylated form in 29 patients and no-PEG in 2 patients); two patients did not accept primary G-CSF prophylaxis and did not develop myelotoxicity. In our study the incidence of grade 3 or 4 neutropenia was 21.2% (95% CI, 9.8-37.5); febrile neutropenia was observed in just one patient (3.0%; 95% CI, 0.1-14.0), with subsequent hospitalization and full recovery. Twenty-two patients (66.6%) underwent primary dexrazoxane prophylaxis, however, cardiotoxicity was absent in both subgroups (0%; 95% CI, 0-8.7%). Two cases (6.1%; 95% CI, 1.0-18.6) of major allergic reaction G3 to docetaxel (generic drug) were observed. No treatment-related death was seen. Overall, the incidence of grade 3 or 4 no hematologic adverse events (AEs), regardless of type, was very low. All grades and 3-4 grades treatment-related AEs are shown in Table 5.

Table 5 Toxicity

		All grades No (%) [95% CI]	*Grade 3-4 No (%) [95% CI]*
Hematologic			
	Neutropenia	12 (36.4) [21.4-53.6]	7 (21.2) [9.8-37.5]
	Febrile Neutropenia	1 (3.0) [0.1-14.0]	1 (3.0) [0.1-14.0]
	Anemia	3 (9.1) [2.4-22.8]	1 (3.0) [0.1-14.0]
	Thrombocytopenia	2 (6.1) [1.0-18.6]	1 (3.0) [0.1-14.0]
	IV antibiotics for NF	1 (3.0) [0.1-14.0]	1 (3.0) [0.-14.0]
Nonhematologic			
	32-months Cardiac toxicity§	0 (0) [0-8.7]	0 (0) [0-8.7]
	Emesis	7 (21.2) [9.8-37.5]	1 (3.0) [0.1-14.0]
	Diarrhea	2 (6.1) [1.0-18.6]	1 (3.0) [0.1-14.0]
	Neurotoxicity	2 (6.1) [1.0-18.6]	1 (3.0) [0.1-14.0]
	Docetaxel Reactions	2 (6.1) [1.0-18.6]	2 (6.1) [1.0-18.6]
	Asthenia	1 (3.0) [0.1-14.0]	0 (0) [0-8.7]
	Mucositis	1 (3.0) [0.1-14.0]	0 (0) [0-8.7]
	Pain	1 (3.0) [0.1-14.0]	0 (0) [0-8.7]

Abbreviations: CI: confidence interval; §Cardiac toxicity: it was defined as LVEF decrease ≥20% points from baseline; LVEF was measured at baseline and at the end of chemotherapy, thereafter every 6 months.

Survival

At a median follow-up of 32 months (range 11-36), one patient (3.0%) developed primary pancreatic tumor and two patients (6.1%) had relapsed: one patient had a pulmonary recurrence and one patient a liver recurrence. Two of 33 patients (6.1%) died, one (3.0%) for breast cancer relapse and one (3.0%) for a secondary cancer. At the time of analysis, the median time to relapse and death was not reached. After 32 months, the estimated 3-year DFS rate was 89.9% (95% CI, 79.0-100) and the 3-year OS rate was 93.8% (95% CI, 85.6-100), as shown in Figures 1 and 2, respectively.

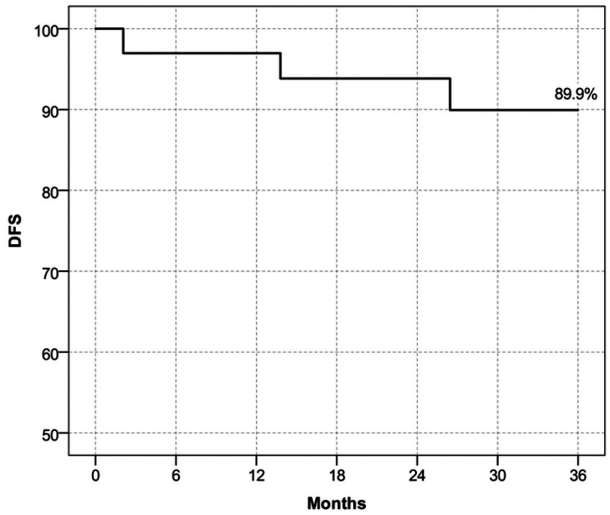

Figure 1 Disease Free Survival (DFS) - Data were analysed by Kaplan-Meier method

Discussion

Adjuvant therapy's benefits are well known in early and operable breast cancer. Several meta-analyses have showed higher efficacy in DFS and OS of anthracyclines and taxanes chemotherapy combinations, either concurrent

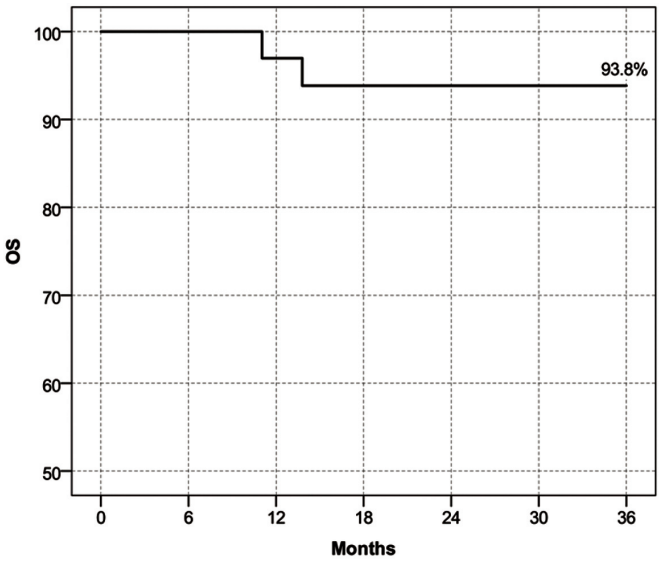

Figure 2 Overall Survival (OS) - Data were analysed by Kaplan-Meier method

or sequential treatments [4, 5, 10]. TAC chemotherapy, combining docetaxel (T) 75 mg/m^2, doxorubicin (A) 50 mg/m2 and cyclophosphamide (C) 500 mg/m^2 IV on day 1 every three weeks for 6 cycles, is one of standard adjuvant regimens indicated by national and international guidelines, such as those developed by AIOM, ESMO and NCCN [11-13].

Concurrent TAC regimen was assessed in four randomized phase III trials: BCIRG 001, GEICAM 9805, BCIRG 005 and NSABP B-30 trials [6-7, 14-15]; the latter study will be excluded from our subsequent considerations because of the shorter duration of the TAC arm in the trial [15].

Martin et al. in BCIRG 001 and GEICAM 9805 trials, the most important studies which compared TAC with FAC regimen (fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 IV on day 1 every 3 weeks for 6 cycles), proved the superiority of docetaxel-based chemotherapy in both node-positive and high-risk node-negative early breast cancer, but at the cost of a greater toxicity [6-7].

BCIRG 005 trial, comparing TAC combination with AC→T sequential regimen (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 IV on day 1 every 3 weeks for four cycles, followed by four cycles of docetaxel 100 mg/m^2 IV every 3 weeks), demonstrated equal efficacy but with different toxicity profile [14].

The two most commonly used anthracyclines are doxorubicin and epirubicin. Anyway, even if doxorubicin and epirubicin are equivalent in terms of efficacy, at similar doses the epirubicin appears to have a better side effects profile than doxorubicin in terms of myelosuppression and cardiotoxicity. More specifically, the equimolar dose ratios of doxorubicin to epirubicin for myelosuppression and cardiotoxicity are 1:1.2 and 1:1.7-2.0, respectively [16].

They are known to cause both short- and long-term cardiotoxicity, including potentially fatal congestive heart failure (CHF). The median cumulative doses at which the two drugs can cause congestive heart failure are respectively 492 mg/m^2 for doxorubicin and 1134 mg/m^2 for epirubicin [17]. The mechanism of cardiotoxicity induced by anthracyclines is not fully understood, however, some pharmacological and toxicological data suggest that cardiotoxicity is caused by the interaction between the anthracycline and the iron ions with the consequent formation of complexes which mediate a cytotoxic mechanism on the myocardium [18]. In support of this mechanism, the use of a substance such as iron chelator dexrazoxane reduces the risk of anthracycline cardiotoxicity [17].

Epirubicin has a lower propensity to produce myelotoxic and cardiotoxic effects than doxorubicin, and its recommended maximum cumulative dose is almost double that of doxorubicin, thus allowing for more treatment cycles and/or higher doses of epirubicin [19].

In view of the high and frequent toxicity associated to TAC regimen, we performed this retrospective study to explore the hypothesis that the use of epirubicin rather than doxorubicin can improve tolerability.

The incidence of grade 3-4 toxicity reported in our study with TEC regimen was very low as compared to that of phase III trials with TAC regimen (BCIRG 001, GEICAM 9805 and BCIRG 005) [6-7, 14]. In particular, grade 3-4 neutropenia and febrile neutropenia (FN), which are usually the most frequent side effects of TAC regimen, were observed in only 21.2% (95% CI, 9.8-37.5) and 3% (95% CI, 0.1-14.0) of our patients, respectively (Tables 5, 6 and 7). In the above mentioned phase III studies, the grade 3-4 neutropenia varied between 50.8-65.5% and febrile neutropenia between 9.6-28.8% (Table 6). Primary G-CSF prophylaxis was permitted in the BCIRG 005 trial but not in BCIRG 001 and GEICAM 9805 trials [14, 6-7]; however, owing to an incidence of neutropenic fever of more than 25% in the TAC group, the protocol in the GEICAM 9805 was amended after 230 patients enrolled [7].

In a randomized phase II trial, AERO B03 trial, the "standard" control arm was TEC regimen: docetaxel 75 mg/m^2 (T), epirubicin 75 mg/m^2 (E) and cyclophosphamide 500 mg/m^2 (C) IV on day 1 every 3 weeks for 6 cycles. Grade 3-4 neutropenia occurred in nine (26%) patients and febrile neutropenia in four (11%) patients; no one cardiac failure was registered [20]. These rates are more similar but slightly higher than those of our study (Table 6).

According to recent indications of ASCO, NCCN and EORTC guidelines [21-23], the prophylactic administration of growth factors is recommended in all patients undergoing chemotherapy with an expected incidence of FN ≥20%. More specifically, the risk of febrile neutropenia associated with TAC schedule is estimated to be 23.8% [24].

Table 6 Literature review and current study

Trial	*Phase*	*No patients*	*Chemotherapy*	*Primary prophylaxis*	*Grade 3-4 neutropenia*	*NF*[α]	*Grade 3-4 cardiotoxicity*
BCIRG 001	III	744	TAC[β]	No	65.5%	28.8%[ε]	0.1%
GEICAM 9805	III	532	TAC	No (amended)	50.8%	9.6%[ζ]	0.6%
BCIRG 005	III	1635	TAC	Yes (permitted)[η]	59.9%	17.40%	0.1%
AERO B03	II randomized	35	TEC75[γ]	Yes (permitted)[θ]	29%	11%	0%
Current study	retrospective	33	TEC60[δ]	Yes (permitted)[ι]	21.4%	3%	0%

Abbreviations and references: [α]NF: febrile neutropenia; [β]TAC: docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 IV on day 1 every 3 weeks for 6 cycles [6]; [γ]TEC: docetaxel 75 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2 IV on day 1 every 3 weeks for 6 cycles [20]; [δ]TEC: docetaxel 75 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 500 mg/m^2 IV on day 1 every 3 weeks for 6 cycles (median doses); [ε]NCI CTC definition 2.0: fever of 38°C or more concomitant with grade 3 or 4 neutropenia [6]; [ζ]The rate of febrile neutropenia was 25.2% among the 111 patients who did not receive primary prophylaxis and 5.5% among the 421 patients who received primary G-CSF prophylaxis [7]; [η]Primary prophylaxis was delivered in just 17% of patients of TAC group [14]; [θ]Primary prophylaxis was delivered in the 80% of patients [20]; [ι]Primary prophylaxis was delivered in the 94% of patients.

Table 7 Comparison between current and previous studies with similar median follow up

	BCIRG 001 (interim analysis) [26]	*Hungarian experience (BCIRG 001) [27]*	*BCIRG 005 (interim analysis) [28]*	*Current study*
Phase	III	III	III	retrospective
Median follow up	33 months	33 months	30 months	32 months
No patients	744	34	1635	33
Chemotherapy	TAC	TAC	TAC	TEC60
Primary prophylaxis	No	No	Yes (permitted)	Yes (permitted)
Grade 3-4 neutropenia	65.1%	76%	60.1%	21.2%
Febrile neutropenia	23.9%	26%	17.9%	3%
Grade 3-4 cardiotoxicity	1.6%	N/A	0.1%	0%
DFS	82%	88%	N/A	89.9%
OS	92%	97%	N/A	93.8%

Abbreviations: N/A: not available

So, the incidence of severe neutropenia and NF in our study was extremely lower than in others (21.2% and 3%, respectively); it was likely due to the substitution of doxorubicin with epirubicin, to a lower median doses of epirubicin (60 mg/m^2) and primary G-CSF prophylaxis in the most of our patients (94%).

As regards cardiotoxicity, in our retrospective study 66% of patients underwent primary dexrazoxane prophylaxis; anyway, none of the patients at a 32 months follow up developed sub-clinical or clinical congestive cardiac failure or any other short- and long-term adverse effects so far, with no difference between the two subgroups (0%; 95% CI, 0-8.7%) (Tables 5, 6 and 7). Furthermore, these observations are consistent with the findings of previous trials when a more similar median follow up, from 30 to 33 months, is considered [26-28] (Table 7).

Percentages of other grade 3-4 side effects were very low, about 0-3%, except for two episodes (6.1%; 95% CI, 1.0-18.6) of major allergic reaction G3 to docetaxel, that was slightly higher than in the other studies; these two patients did not received the standard premedication with dexamethasone at a dose of 8 mg orally twice a day for 3 days (6 doses) to reduce the risk of acute hypersensitivity reactions commonly associated with docetaxel therapy (Table 5). A dose reduction was performed in just 21.2% of patients and the overall mean dose-chemotherapy reduction was 4.1% (Table 4). Actually, the starting and final median doses in our trial do not change (Tables 2 and 3).

The thirty-two months follow up period considered in this study allowed us to analyze the DFS and OS data of the patients. The 3-year DFS and OS were 89.9% (95% CI, 79.0-100) and 93.8% (95% CI, 85.6-100), respectively (Figures 1 and 2).

The median doses of epirubicin used in our TEC regimen are lower than those commonly recommended (75, 90 and 100 mg/m^2). Epirubicin at doses of 50 mg/m^2 should be considered sub-optimal when compared to the 100 mg/m^2 dose [25]. The role of 60 mg/m^2 epirubicin dose is uncertain. In one trial, comparing two dose levels of

epirubicin (60 mg/m^2 vs 100 mg/m^2) in adjuvant setting, it was showed less efficacy of epirubicin at lower doses [29].

Nevertheless, in 1999 Mouridsen H et al. of the Danish Breast Cancer Group demonstrated that adjuvant CEF (epirubicin 60 mg/m^2) was superior to CMF (cyclophosphamide, methotrexate and 5fluorouracil) in terms of survival in premenopausal patients with intermediate and high-risk breast cancer (93% vs 83%; $p < 0.01$) [30].

However, this probably is the first time that epirubicin at the dose of 60 mg/m^2 has ever been added to concurrent docetaxel-containing chemotherapy. Although the median follow up of the present study was too short to calculate median DFS and OS times, our estimated 3-year survival data resembled those observed in the trials using TAC regimen when a more similar median follow up is considered [26-27] (Table 7).

Conclusions

Our study has some limitations: it's a retrospective non-comparable trial and based on a small sample size. Chemotherapy doses and prophylactic treatments were chosen at investigator's discretion. The follow up was too short at the time of analysis. However, it may give us some suggestive indications. This study clearly shows that TEC (epirubicin 60 mg/m^2) treatment is associated to a very low risk of grade 3-4 toxicity. It has an acceptable and manageable toxicity as compared to both TAC and TEC (epirubicin 75 mg/m^2) regimens. It is feasible and well tolerated adjuvant chemotherapy in early and operable breast cancer. Our results are just exploratory, but indicate that TEC 60 mg/m^2 regimen could be selected for further assessments in randomized phase II and/or III trials.

Conflict of interest

The authors wish to express that they have no conflict of interest.

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