A randomized phase II study of combination, alternating and sequential regimens of doxorubicin and docetaxel as first-line chemotherapy for women with metastatic breast cancer

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Background: This randomized phase II study was conducted to evaluate the efficacy of doxorubicin and docetaxel (DOC) administered either as a combination, an alternating or a sequential regimen in women with metastatic breast cancer. Secondary objectives included overall response, time to progression, survival and safety.

Patients and methods: Patients with breast cancer \( n = 123 \) were randomized to receive doxorubicin and DOC either in combination (60 mg/m\(^2\) of each drug), or by alternated or sequential schedule (100 mg/m\(^2\) DOC and 75 mg/m\(^2\) doxorubicin) every 3 weeks for a maximum of eight cycles as first chemotherapy for stage IV disease. A second randomization allocated patients from each arm to receive prophylactic oral ciprofloxacin or no therapy to prevent febrile neutropenia.

Results: Patients received a median of eight cycles. In an intention-to-treat analysis, the overall response was 63%, 52% and 61% in the combination, alternating and sequential schedules, respectively. Corresponding rates of complete response were 15%, 14% and 11%. Grade 4 neutropenia was common in all arms (81%) and, together with febrile neutropenia, was significantly more frequent with the combination. Prophylaxis with ciprofloxacin did not reduce the incidence of febrile neutropenia or infection. Other frequent non-hematological adverse events included alopecia, nausea, vomiting, stomatitis and asthenia. Congestive heart failure only occurred in the combination arm (10%).

Conclusion: All three schedules are feasible and endowed of good therapeutic activity. In view of the more pronounced toxicity and the risk of cardiac events because of the higher exposure to doxorubicin, the combination should be least favored when treating women with metastatic breast cancer. Prophylaxis with ciprofloxacin was ineffective and is not recommended.

Key words: docetaxel, doxorubicin, breast cancer

Introduction

Anthracycines and the taxanes docetaxel (DOC) and paclitaxel are the classes of cytotoxic drugs affording the best therapeutic results for women with breast cancer [1, 2]. In particular, DOC showed superior antitumor activity over doxorubicin [3], and studies showed that it also had antitumor activity in women with anthracycline-resistant disease [4]. Lack of complete clinical cross-resistance justified the conduct of studies combining the two drugs in the AT (doxorubicin and docetaxel) [5] and in the TAC regimens (docetaxel, doxorubicin and cyclophosphamide) [6]. A phase III comparison in metastatic breast cancer showed superior activity and efficacy of AT over the standard doxorubicin and cyclophosphamide [7]. For TAC, superior antitumor activity did not translate into significant improvement in median time to progression and overall survival over classical FAC regimen (fluorouracil, doxorubicin and cyclophosphamide) for women with metastatic breast cancer [8]. Instead, in the adjuvant setting the TAC regimen improved the disease-free survival (82% versus 74%) over FAC [9].

Metastatic breast cancer is almost always an incurable disease. Among relevant determinants of such unfavorable course, acquired multidrug resistance plays an undisputed role. Traditionally, combination therapy has been developed to try and circumvent acquired resistance by the concomitant application of drugs with
different mechanisms of action and non-overlapping toxicities. However, it is still underdetermined what is the best approach for the optimal application of non-cross-resistant drugs. The Goldie and Coldman hypothesis [10] calls for alternating non-cross-resistant drugs as early as possible. According to Norton and Simon [11], tumor regression is proportional to the dose intensity and the sequential administration of the drugs. We thought that the availability of non-cross-resistant drugs endowed of high activity, such as DOC and doxorubicin, could offer an excellent opportunity to test in patients the respective merits and limits of different schedules of administration. The topic is of present relevance also in view of the maturing of data from adjuvant and neo-adjuvant studies in which different schedules of DOC-containing regimens are applied [9, 12]. We here report a phase II study in which women with metastatic breast cancer were randomized to receive DOC and doxorubicin in combination, in an alternating schedule or in sequence.

**Patients and methods**

From November 1996 to January 2000, 123 women aged 18–70 years were enrolled onto this open-label randomized phase II trial. The study was conducted in accordance with the Declaration of Helsinki after approval of the ethical committees of the nine participating centers. Written informed consent was obtained from all patients.

The primary objective of the study was the rate of complete response in the three groups of treatment. The planned sample size of 41 patients per arm was determined according to Fleming’s two-stage design. It was assumed that no treatment schedule would be of further interest if the complete response rate was <5%. The sample size allowed for testing of the null hypothesis (H0; the true complete response rate is <5%) versus the alternative hypothesis (HA; the true complete response rate is >20%) with a power of 93%. Secondary objectives included overall response, time to progression (TTP), survival and safety.

Another objective of the study was to test whether oral prophylactic antibiotic therapy with ciprofloxacin (500 mg b.i.d. from day 7 to 14) could drastically reduce the frequency of febrile neutropenia which was reported to account for ~40% of the patients and 13% of cycles when doxorubicin was given concomitantly with DOC. Allocation to receive or not receive oral ciprofloxacin was randomly carried out after stratification for chemotherapy regimen. If the study could be completed with all the patients required for assessing anti-cancer treatment effectiveness, two groups of 20 patients, corresponding to about two groups of 100 cycles, could be allocated to oral ciprofloxacin or not in the concomitant arm. This number of cycles could allow to detect a decrease of febrile neutropenia from 13% to 2.5%, with a two-sided significance level of 5% and a statistical power of 80%.

Entry criteria required histologically confirmed measurable metastatic disease and performance of a biopsy in case of a single metastatic lesion. Other requirements included: performance status 0 to 2 [World Health Organization (WHO) scale]; normal organ function [i.e. normal total bilirubin, AST and ALT <2.5-fold the upper limits of normal (ULN), alkaline phosphatase <5 ULN, neutrophil count ≥2 × 10^9/l, platelets ≥100 × 10^9/l, hemoglobin ≥10 g/dl, creatinine <1.6 mg/dl; normal left ventricular ejection fraction (LVEF) as measured by radionuclide angiography or echocardiography. No prior chemotherapy for metastatic disease or concomitant bisphosphonates were allowed. Patients could have received adjuvant chemotherapy provided that the total dose of delivered anthracyclines was no more than 240 mg/m^2 of doxorubicin equivalents delivered at least 1 year before study entry. For the purpose of calculating prior exposure to anthracyclines, 1 mg of doxorubicin was considered equicardiotoxic to 1.8 mg of epirubicin [13], or to 0.3 mg of mitoxantrone. Previous radiotherapy, hormonal therapy (either as adjuvant or for metastatic disease) or surgery were allowed. Patients were excluded in presence of pre-existing peripheral neuropathy ≥G2, central nervous system involvement, prior malignancies (other than non-melanoma skin cancer or excised cervical carcinoma in situ), pregnancy or in absence of adequate contraception.

**Treatment plan**

Patients in the combination arm received doxorubicin (60 mg/m^2) plus DOC (60 mg/m^2) with 1-h interval between drugs; patients in the alternating and in the sequential regimen received doxorubicin (75 mg/m^2) and DOC (100 mg/m^2 infused over 1 h) beginning with DOC for the alternating regimen (four cycles of DOC alternated with four cycles of doxorubicin), and with doxorubicin for the sequential regimen (four cycles of doxorubicin followed by four cycles of DOC) for a maximum of eight cycles. Corticosteroid premedication was given with DOC administration (8 mg of oral dexamethasone at 13, 3 and 1 h before DOC infusion and at 12, 24, 36 and 42 h after DOC infusion). In case of repeated febrile neutropenia (see also below), grade 3 diarrhea, grade 3 stomatitis, grade 3 nausea and vomiting (despite adequate preventive or curative medication), DOC was reduced to 75 mg/m^2 and doxorubicin to 60 mg/m^2 in the alternating and sequential regimens; while doxorubicin was delivered at 50 mg/m^2 without modifying DOC in the combination arm. Only reduction of doxorubicin (to 60 mg/m^2 in the alternating and sequential arms and to 50 mg/m^2 in the combination arm) was required for grade 4 thrombocytopenia. In all regimens in presence of grade 2 peripheral neuropathy only DOC reduction was planned. Both drugs were decreased in patients with impaired liver function.

In order to avoid cardiac toxicity the maximum cumulative dose of doxorubicin equivalents was initially set at 550 mg/m^2. In March 1999 the limit was decreased to 480 mg/m^2 in the light of the observed cardiac toxicity.

Patients randomized to antibiotic prophylaxis received ciprofloxacin, 500 mg orally twice daily from day 7 to day 14 of each cycle to evaluate the prevention of febrile neutropenia defined as grade 4 neutropenia with fever ≥38°C in three determinations during a 24-h period, or a single elevation above 38.5°C. Hospitalization was always performed for the first cases of febrile neutropenia at the beginning of the study. Following cases were treated at home whenever possible and admitted to hospital if fever >38.5°C persisted for more than 3 days. Patients not randomized to antibiotic prophylaxis could receive antibiotic prophylaxis only following febrile neutropenia in a previous cycle. Recombinant granulocyte colony-stimulating factor (G-CSF) was allowed only in cases of repeated episodes of febrile neutropenia.

**Patient and treatment evaluation**

Pre-study evaluation included patient’s medical history, physical examination, chest X-ray or computed CT scan, complete blood cell count (CBC), liver and kidney tests, abdominal echography or computed CT scan, bone scan, ECG and measurement of LVEF. In case of liver disease CT scan was used to assess response. Response according to WHO criteria was assessed every other cycle [14] and toxicity according to the National Cancer Institute common toxicity criteria (NCI CTC) scale [15] at each visit.
Biochemistry assessments were made before every cycle, while CBC was performed weekly and repeated every other day until recovery in case of grade 4 neutropenia or thrombocytopenia. LVEF was assessed after a cumulative dose of doxorubicin of 300 mg/m² and repeated before every cycle once a cumulative dose of 400 mg/m² was reached.

All efficacy and safety analyses were performed on the intention-to-treat population, defined as the patient population who started at least one cycle of doxorubicin or DOC. Time to progression was calculated starting from the date of randomization to the date of first progression. Survival was the time from randomization to death from any cause. The response rates and rates of toxic events were compared between the three groups with the Fisher’s exact test, while continuous variables were summarized with at least the median and the range.

## Results

### Patient characteristics

Of the 123 patients enrolled, 121 received study treatment. Among enrolled patients, 13 (11%) were found not to meet eligibility criteria (including absence of measurable disease according to WHO criteria in nine and altered laboratory findings in the other three patients). Six, five and two of these 13 patients were enrolled into the alternating, combination and sequential arms, respectively. Patient characteristics were well balanced between arms (Table 1). Median age was 53 years (range 24–69) and the median WHO performance was 0 (range 0–1). Fifty-three patients (44%) had prior adjuvant chemotherapy, including anthracyclines in 16 (13%). Visceral involvement was present in the majority of patients, and liver metastases were present in 46, 43 and 40% of patients in the combination, alternating and sequential schedules, respectively.

### Therapeutic effects

Overall, the median number of delivered cycles was eight, and the median relative dose intensity was ≥0.9 for each drug in each arm. Toxicity caused delay of treatment in 16% of cycles in each arm, and <10% of cycles were delivered at reduced dose of either drug. Discontinuation of treatment due to adverse events was reported in 14 patients (11.5%): two treated with alternating, seven with combination and five with sequential treatment. Patients in the combination arm received a higher median total dose of doxorubicin (460 mg/m²) than those in the alternating (294 mg/m²) and sequential (297 mg/m²) regimens. Corresponding median cumulative dose of DOC was respectively 468, 392 and 388 mg/m² in the three arms.

### Antitumor activity

According to intent-to-treat analysis, the overall response was 63% (95% CI 47–77%) with the combination, 52% (95 CI 37–68%) with the alternating and 61% (95% CI 43–76%) with the sequential regimen (Table 2). Corresponding rates of complete response were 15%, 14% and 11%, respectively. No statistically significant difference among treatments was present. At a median 22 months of follow-up, median time to progression (TTP) was 36 weeks (95% CI 28–49 weeks) for the combination, 34 weeks (95% CI 27–66 weeks) for the alternating schedule and 33 weeks (95% CI 28–42 weeks) for the sequential schedule. Only a minority of patients progressed while on therapy (10%, 19% and 13% with combination, alternating and sequential regimens, respectively).

However, a high proportion of patients (44% in the combination arm and 29% in each of the other two arms) were censored in the analysis of TTP because they received a different therapy (either hormonal or chemotherapy) even in the absence of progression at end of study treatment. With respect to survival, with 41 patients per group the three groups were not noticeably different. The estimated overall survival probabilities were 90% at 1 year, 62% at 2 years and 46% at 3 years. The overall median survival time was 34 months (95% CI 25–46 months).

### Toxicity

Grade 4 neutropenia was the most frequent toxicity and occurred in 83%, 88% and 71% of patients in alternating, combination and sequential arms, respectively. Febrile neutropenia was signifi-

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### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Comb</th>
<th>Alt</th>
<th>Seq</th>
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</thead>
<tbody>
<tr>
<td>No. of patients randomized</td>
<td>42</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>No. of patients treated</td>
<td>41</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>No. of patients eligible</td>
<td>36</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>54 (30–68)</td>
<td>52 (30–69)</td>
<td>54 (24–67)</td>
</tr>
<tr>
<td>Median WHO PS (range)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Prior (neo) adj CT (%)</td>
<td>19 (46%)</td>
<td>17 (40%)</td>
<td>17 (45%)</td>
</tr>
<tr>
<td>Prior anthracyclines (%)</td>
<td>6 (15%)</td>
<td>6 (14%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Visceral involvement</td>
<td>27 (66%)</td>
<td>31 (74%)</td>
<td>32 (84%)</td>
</tr>
<tr>
<td>Liver involvement</td>
<td>19 (46%)</td>
<td>18 (43%)</td>
<td>15 (40%)</td>
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<tr>
<td>≥3 organs involved</td>
<td>13 (32%)</td>
<td>22 (52%)</td>
<td>17 (45%)</td>
</tr>
</tbody>
</table>

adj CT, adjuvant chemotherapy; Alt, alternating arm; Comb, combination arm; Seq, sequential arm; WHO PS, World Health Organization performance status.

### Table 2. Therapeutic effects

<table>
<thead>
<tr>
<th></th>
<th>Comb (41 patients)</th>
<th>Alt (42 patients)</th>
<th>Seq (38 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>15%</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>PR</td>
<td>49%</td>
<td>38%</td>
<td>50%</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>63%</td>
<td>52%</td>
<td>61%</td>
</tr>
<tr>
<td>95% CI</td>
<td>47, 77%</td>
<td>37, 68%</td>
<td>43, 76%</td>
</tr>
<tr>
<td>Median TTP, weeks</td>
<td>36</td>
<td>34</td>
<td>33</td>
</tr>
</tbody>
</table>

Alt, alternating arm; CI, confidence interval; Comb, combination arm; CR, complete response; ORR, overall response rate; PR, partial response; Seq, sequential arm; TTP, time to progression.
significantly higher ($P<0.05$) in the combination arm (22% versus 7% in the alternating and 0% in the sequential). An analysis of the neutropenia associated with single-agent doxorubicin and DOC in the alternating and sequential arms indicated that severe episodes occurred evenly spread throughout the entire course of treatment without indication of cumulative toxicity, and that the two drugs caused similar effects at the selected doses. Antibiotic prophylaxis did not prevent episodes of febrile neutropenia (14% episodes in cyprofloxacin-treated patients versus 6% in the control arm) or infections. Grade 3/4 infections (2%) were only observed with the combination arm. No septic deaths were reported (Table 3).

The combination regimen was also associated with higher incidence of grade 3/4 stomatitis (12% versus 5% in both alternating and sequential arms). Other grade 3/4 toxicities were diarrhea, nausea, vomiting and asthenia (Table 4). All of them occurred with similar frequency in the three arms of therapy.

### Cardiac toxicity

Cardiac toxicity was more common in the combination arm with 32% events of grade 1 and 2 versus 5% events of grade 1 in the alternating arm and 11% events of grade 1 and 2 in the sequential arm. No grade 3 and 4 cardiac toxicity events were reported except in the combination arm, in which four episodes (10%) of congestive heart failure (CHF) were observed (Table 5). All the patients who developed CHF had received a cumulative dose of doxorubicin equivalents, including prior adjuvant anthracyclines, of 480 mg/m$^2$ (487 mg/m$^2$ in one patient). One patient also had received left breast adjuvant radiotherapy and recovered from cardiac heart failure after 1 year. A second patient had received previous chemotherapy with epidoxorubicin (210 mg/m$^2$) as adjuvant treatment 3 years before enrolment and she died from progression of disease. A third patient was known to have mild arterial hypertension. The last patient had no cardiac risk factors. All patients but one recovered from CHF with adequate cardiac medication.

### Discussion

Taxanes and anthracyclines are increasingly used as the option of choice for treating women with breast cancer. In particular, DOC and doxorubicin have outstanding antitumor activity and efficacy,
and lack complete clinical cross-resistance [4]. However, these drugs are being tested in clinical trials as therapy for metastatic disease or as adjuvant/preoperative systemic treatment without a formal assessment of the most convenient schedule [2, 6, 9, 16], thus justifying in-depth analyses to define the optimal modality for their administration.

Common clinical wisdom supports the concomitant application of drugs endowed of different mechanisms of action and non-overlapping toxicity to decrease the probability of resistance. However, over the years theories suggested that alternating [10] or sequentially applying non-cross-resistant drugs/combinations [11] may afford better therapeutic results. In the past, a landmark work by Bonadonna et al. [17] indicated superior efficacy when doxorubicin and combination therapy with cyclophosphamide, methotrexate and fluorouracil (CMF) were administered sequentially rather than in an alternating fashion as adjuvant therapy for women with high-risk breast cancer. To our knowledge, this is the first trial directly addressing the question of the antitumor activity and tolerability of combined, alternating or sequential schedules of administration of DOC and doxorubicin. The primary end point of the study was to rank rates of complete response in patients never treated with chemotherapy for metastatic disease while attempting to achieve activity as high as described in other trials of taxanes and anthracyclines [18] or vinorelbine and doxorubicin [19] in untreated advanced breast cancer.

Many reports describe the combined use of DOC and doxorubicin [5, 6, 16, 20], while fewer deal with their sequential delivery [21, 22], and one preliminary report describes the use of either sequential or alternating modality of administration [23]. For our trial, we used the highest doses feasible without prophylactic G-CSF whenever doxorubicin and DOC were used as single agents [24]. For the combination, we referred to the phase I experience [5]. Of the two schedules recommended for further development in that trial, we adopted the one delivering both drugs at the same dose of 60 mg/m² [5].

For each schedule of administration, the overall antitumor activity (63%, 52% and 61% in the combined, alternating and sequential arms, respectively) and the rate of complete response (from 15% with the combination to 11% with the sequential regimen) fell within the boundaries of the activity reported in other trials of DOC and doxorubicin, in which the observed overall response rate ranged from 40 and 77% [6, 16, 20, 21, 25, 26]. Although the study failed to meet the primary objective that was to achieve a CR rate of 20% in at least one treatment group, the other findings of this multicenter study are very positive. Given the high proportion of patients in our study having predominant visceral disease (74%) and at least three organs involved (43%), the results should be viewed as an indication of good therapeutic effect for each tested regimen. The antitumor activity of each tested regimen must be considered in view of the fact that the combination approach involved the administration of almost twice as much doxorubicin and a slightly higher total dose of DOC than the other two regimens. Time to progression was of the same order of magnitude for each regimen, and of value similar to that reported for the TAC [8] and for the AT combination [7] in two randomized phase III trials. However, we feel that our data should be interpreted with caution given that most patients were censored from analysis because they underwent different therapies after end of study treatment even in the absence of progression.

Data on tolerability offer several opportunities for discussion. All regimens were feasible, as expected from other reports [6, 16, 20, 21, 25, 26], and as shown by the possibility of delivering a median eight cycles per patient, with a median dose intensity >90% of the planned intensity for each drug with each regimen. When considering hematological toxicity, neutropenia was most prominent. Overall, a high rate of severe toxicity was observed in each arm. However, the combination was associated with more frequent episodes of febrile neutropenia and a 2% rate of moderate–severe infection. Of interest in this respect, the study also addressed in a randomized fashion the question whether the use of prophylactic ciprofloxacin could prevent or reduce incidence and severity of febrile neutropenia and infections. Such a measure was proposed by other investigators concerned by the incidence of severe neutropenia associated with DOC administration [27]. Prophylactic ciprofloxacin did not contribute to any reduction of the episodes of febrile neutropenia. In view of the risk of selecting resistant bacteria and the cost of such intervention, our study does not support the adoption of this measure.

The higher rate of febrile neutropenia seen with the combination regime could be simply due to the higher total dose of delivered doxorubicin. However, it could also be due to a toxic enhancement between doxorubicin and DOC. While this was described as a possibility due to pharmacokinetic interaction for the combination of doxorubicin and paclitaxel, that also is associated with a high rate of severe neutropenia [18]. Data about pharmacokinetic interaction between doxorubicin and DOC are discordant. Indeed, Itoh et al. reported a sequence-dependent hematological toxicity with DOC and doxorubicin even in the absence of any meaningful pharmacokinetic interference between the two drugs [26]. Another pharmacokinetic study of similar design did confirm the lack of effects of DOC on plasma exposure to doxorubicin and metabolites, but failed to show any effect of sequence, and documented that doxorubicin caused an increased exposure to DOC [28]. Together with the higher total dose of doxorubicin delivered, this possible interaction might explain the higher hematological toxicity of the combination regimen.

Non-hematological toxicity was similar in the three arms of treatment and in agreement with the data reported [6, 16, 20, 21, 25, 26], although a slightly higher incidence of moderate/severe stomatitis occurred with the combination. We only observed one case of grade 4 hand–foot syndrome among patients enrolled in the sequential arm. This is different from the report of Miller et al. [21], who described grade 3 and 4 hand–foot syndrome in 42% of patients receiving sequential doxorubicin and DOC. In considering the much lower incidence of toxicity in our study, it should be noted that substantially higher doses of corticosteroids before and after chemotherapy were adopted in the present trial when delivering DOC.

A final consideration about tolerability is related to the observed cardiac effects. Serial cardiac assessments were performed to prevent or recognize early myocardial toxicity due to the administration of the two drugs. The results clearly show a significantly higher
increased risk shows up at a total doxorubicin dose because of pharmacological interaction, and 18 weeks after discontinuation of anthracycline [29]. In addition, reported at 7% at 550 mg/m², that tends to occur between 4 and 18 weeks after discontinuation of anthracycline [29]. In addition, previous irradiation to the left chest wall or other risk factors such as hypertension could have contributed to the episodes of cardiac toxicity observed in our trial. However, the rate of CHF we report here is apparently in excess of that in other studies of DOC combined with doxorubicin. Nabhältz et al. [7] described a 3% incidence of CHF with AT (doxorubicin with DOC), and more recently only 2.4% of CHF was reported in association with the TAC combination in women with metastatic breast cancer [8] and 4% when the same combination was applied for early breast cancer [9]. However, in all the above studies, the total dose of delivered doxorubicin was always lower than that administered in the present trial. In the study of AT versus AC it was 378 mg/m² [7], while it was about 300 mg/m² when the TAC regimen was used for women with metastatic breast cancer [8] or as adjuvant therapy for operable breast cancer [9]. While this observation again points to the different and higher total dose of doxorubicin delivered in our study as the main reason for the incidence of clinical cardiac toxicity, it should be noted that the other taxane, paclitaxel, may cause increased cardiac toxicity because of pharmacological interaction, and that this increased risk shows up at a total doxorubicin dose >360–380 mg/m², as we delivered with DOC in the present study. For this reason, a toxic interaction between doxorubicin and DOC should also be taken into account as a possible contributing factor at high total dose of concomitantly delivered anthracycline. Such a possibility is consistent with a preclinical study reporting that higher concentrations of myocardial doxorubicin and doxorubinolin in mice could be found after delivery of doxorubicin and DOC in combination than after administration of single-agent doxorubicin [30]. Furthermore, a recent report indicated that in human myocardial tissue both paclitaxel and DOC cause induction of metabolic transformation of doxorubicin to cardiotoxic species, even though DOC does so within a narrower window of enzymatic activity than paclitaxel, thus projecting for a lower impact than paclitaxel on clinical effects [31].

In summary, our study showed that doxorubicin and DOC afford good therapeutic results independently of the schedule of administration. However, the therapeutic window of the combination was worse than that of the alternating and sequential regimens because of significantly more hematological and cardiac toxicity, most likely due to the higher total dose of delivered doxorubicin. Finally, prophylaxis with ciprofloxacin was not effective in decreasing the incidence of febrile neutropenia. In view of these findings, the combination of doxorubicin and DOC would appear as the least favored for women with metastatic breast cancer. The conclusion whether the combination should be the least favored regimen also for women with operable breast cancer will have to await the results of three major ongoing studies in which doxorubicin and DOC are applied either in sequence or in combination as adjuvant systemic therapy.

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References


