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ORIGINAL ARTICLE

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# Irinotecan combined with docetaxel in pre-treated metastatic breast cancer patients: a phase II study

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**Abstract** *Purpose*: This is a phase II study where a novel chemotherapy combination was tested in pre-treated breast cancer patients: docetaxel and irinotecan have already been established as agents for breast and colorectal cancer, respectively. *Methods*: Forty-eight (median age 54 years, range 26–77 year) patients, all evaluable, were enrolled. All patients had been pre-treated with anthracycline-combined chemotherapy, 30 of whom were also treated with paclitaxel and 2 with docetaxel. World Health Organization (WHO) performance status was 0–2. The dominant metastasis was in the liver (54.17%), in the lungs (27.08%), in soft tissues (12.50%) and in the skeleton (6.25%). Treatment involved irinotecan infusion 200 mg/m$^2$ for 90 min and docetaxel infusion 80 mg/m$^2$ for 90 min, repeated once every 3 weeks. *Results*: Twenty-five (52.08%, 95% confidence interval [CI] 37.95–66.21) patients showed responses: 3 complete (6.25%, 95% CI 0–13.05) and 22 (45.83%, 95% CI 31.74–59.92) partial; the most responsive metastases were observed at the liver site (53.85%). Grade 3 and 4 neutropenia was observed in 18 patients (37.50%); 14 (29.17%) patients developed anaemia and three (6.25%), thrombocytopenia. Concerning non-haematologic toxicity, alopecia and fatigue were common; grade 3 diarrhea was observed in only one (2.08%) patient. *Conclusion*: The irinotecan-docetaxel combination produces quite a high response rate in pre-treated advanced breast cancer patients.

**Keywords** Irinotecan · Docetaxel · Breast cancer

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## Introduction

Advanced breast cancer can be treated effectively by chemotherapy. Several agents in combination achieve medium or high response rates [1–4]. Anthracyclines and taxanes are the most effective cytotoxic drugs: [5–7] a long survival and a good quality of life have been reported, [8–11], even though advanced metastatic breast cancer remains incurable. There are other cytotoxic agents for certain cancers, the newest of which may also have a use in clinical practice for other malignancies [12–16]. In order to find alternative cytotoxic combinations which may be beneficial or even more effective, the testing of new drugs is worthwhile. Camptothecines, a class of cytotoxic agents which have had no place in breast cancer chemotherapy, have been shown to be effective in other tumours [17, 18]. Irinotecan is a semi-synthetic derivative of camptothecin which produces a cytotoxic effect through interaction with, and stabilization of, DNA/topoisomerase-I cleavable complexes by the active metabolite SN-38. The collision of the transcription apparatus and the stabilization of cleavable complex cause damage and lead to cell death [19, 20]. In the present study, we selected irinotecan in order to combine it with docetaxel, an agent known for its effectiveness in advanced breast cancer [21–26]. A previous phase I study established the maximum tolerated dose (MTD) and the acceptable effective dosage of the combination [27]. A recent publication [28] described the

effectiveness of single-agent irinotecan as chemotherapy in patients with metastatic breast cancer refractory to anthracyclines and taxanes. The responses observed suggest the eligibility of irinotecan in combination with other effective agents in further trials. In principle, the combination of docetaxel with irinotecan is justified since each agent has a different mechanism of action and different adverse reactions.

## Patients and methods

### Eligibility criteria

Eligibility criteria included: histologically confirmed breast cancer, prior treatment without response, stable-disease (regression or progression of 25% of measurable disease or recurrence of disease after prior treatment), bidimensionally measurable disease on physical examination, X-rays, ultrasound or computed tomography (CT) scan, World Health Organization (WHO) performance status of 0–2, expected survival≥12 weeks, adequate bone marrow reserve (leukocyte count≥ 3,500/μl, platelet count≥100,000/μl and haemoglobin≥10 g/dl), adequate renal function (serum creatinine ≤ 1.5 mg/dl), and liver function (serum bilirubin ≤ 1.5 mg/dl and serum transaminases ≤ three times the upper limit of normal [or ≤ five times the upper limit of normal in cases of liver metastases]); age≥18 years. Patients with central nervous system (CNS) involvement or with secondary malignancy were excluded. This study was conducted with the approval of our institutional review board/ethical committee, and all patients gave their informed consent before enrollment.

Both agents were infused, starting with irinotecan at a dose of 200 mg/m$^2$ for 90 min in normal saline, followed by the docetaxel 80 mg/m$^2$ for another 90 min. Pre-medication with ondansetron (8 mg), dexamethasone (8 mg) and diphenhydramine (50 mg) was given 1 h before treatment started and was repeated every 4 h the first day. Dexamethasone was also given once the second and third day. Ranitidine was also administered in normal saline at the beginning of the cytotoxic drug infusion. The drugs were administered the first day and the plan was repeated every 21 days for a total of six courses. Patients would refrain from treatment in cases of disease progression or unacceptable toxicity. Hemopoietic growth factor (G-CSF) was not given prophylactically but only when grade 3 or 4 toxicity appeared between the 6th and 8th days.

### Baseline and treatment assessment and response evaluation

Clinical and laboratory evaluation was performed at the end of the 3rd and 6th cycle or whenever there were clinical signs of disease progression. Response and toxicity were assessed using the standard WHO criteria. Complete response (CR) was considered to be the complete disappearance of any sign of demonstrable disease, partial response (PR) as ≥ 50% reduction of measurable disease and stable disease, < 50% decrease or < 25% increase of measurable disease. Duration of response was measured from the documentation of response (CR or PR) to progressive disease. Time to tumour progression (TTP) was measured from the time of the first dose administration to disease progression. The determination of objective response on CT was performed by two independent radiologists and two experienced oncologists.

Before study entry, all patients underwent the following: physical examination, tumour measurement or evaluation, WHO performance status, ECG, full blood count, liver and renal function tests, and urinalysis. Staging was determined by chest and abdominal CT scans, bone scan, and occasional magnetic resonance imaging. Blood count, blood urea and serum creatinine were measured before each treatment administration and 7 days after.

## Results

Forty-eight patients with advanced breast cancer were enrolled in the study between December 2001 and September 2003. All patients were evaluable for response and toxicity. The patients' characteristics at baseline are shown in Table 1; median age was 54 years (range 26–77) and WHO performance status was 0–2. All patients had undergone prior chemotherapy with an anthracycline-containing regimen which included taxanes in 32 patients; thirty of the latter patients received paclitaxel

**Table 1** Patients' characteristics at baseline

| | | No. | Percentage |
|---|---|---|---|
| No. of patients enrolled | | 48 | 100 |
| No. of patients evaluable | | 48 | 100 |
| Age (years) | | | |
| Median | 54 | | |
| Range | 26–77 | | |
| < 50-years-old | | 22 | 45.83 |
| > 50-years old | | 26 | 54.17 |
| Performance status (WHO) | | | |
| 0 | | 8 | 16.67 |
| 1 | | 28 | 58.33 |
| 2 | | 12 | 25.00 |
| Prior chemotherapy | | | |
| Anthracycline-containing | | 48 | 100 |
| Paclitaxel-based | | 30 | 62.50 |
| Docetaxel-based | | 2 | 4.17 |
| Disease-free interval after mastectomy (year) | | | |
| Median | 3 | | |
| Range | 1–7 | | |
| Dominant metastatic sites | | | |
| Liver | | 26 | 54.17 |
| Lung | | 13 | 27.08 |
| Soft tissue | | 6 | 12.50 |
| Skeletal | | 3 | 6.25 |

and two, docetaxel. The prior chemotherapy was given as treatment for advanced metastatic disease. The chemotherapy in the present trial started 2–6 months after the end of first- or second-line treatment. The primary sites of dominant metastases were in the liver (26 patients), in the lungs (13) in soft tissues (6) and in the skeleton (3 patients).

### Response

Median follow-up was 12 months (range 6–26 months). Objective responses were observed in 25/48 (52.08%, 95% confidence interval [CI] 37.95–66.21)) patients. Three (6.25%, 95% CI 0–13.05) patients achieved CR as indicated by a CT-scan; one of these patients had abdominal disease with ascites before treatment and the other two had lung deposits. Remission lasted for 10–12 months. Partial response was seen in 22 (45.83%, 95% CI 31.74–59.92) patients. With respect to dominant metastasis, the partial response distribution was 14/26 (53.85%) patients with liver metastases, 5/13 (38.46%) with lung metastases and 3/6 (50%) with soft tissue disease. There was no difference in objective responses between pre- and post-menopausal women. Median duration of response was 7 months (range 2–10 months). Response rates are indicated in Table 2.

### Survival data

Twenty-four patients (50%) were still alive at the end of the study with a median follow-up of 12 months (range 6–26 months). Median time to disease progression was 8 months (range 4–12 months) and median survival time was 9 months (range 2–20+ months)

**Table 2** Response

| Response | No. of patients | Percentage | CI |
|---|---|---|---|
| Response duration (months) | | | |
| Median | 7 | | |
| Range | 2–10 | | |
| Overall response (complete + partial) | 25/48 | 52.08 | 95% CI 37.95–66.21 |
| Complete response (abdominal) | 3/48 | 6.25 | 95% CI 0–13.05 |
| Partial response | 22/48 | 45.83 | 95% CI 31.74–59.92 |
| Liver | 14/26 | 53.85 | |
| Lung | 5/13 | 38.46 | |
| Soft tissue | 3/6 | 50.00 | |
| Stable disease | 19/48 | 39.58 | |
| Disease progression | 4/48 | 8.33 | |

### Toxicity

Toxicity was acceptable and there were no deaths related to adverse reactions. The main adverse reaction was the myelotoxicity: neutropenia in 18 (37.50%) patients: 15 (31.25%) and 3 (6.25%) patients with grade 3 and 4 neutropenia, one (2.08%) of whom had febrile neutropenia, respectively. Concerning non-haematologic toxicity, alopecia and asthenia were common, while nausea, vomiting and diarrhea (no particular regimen was used for the latter, but three patients had 1-day hydration support) were not. Treatment was postponed in 3 (6.25%) patients and 18 patients had to be supported by G-CSF during days 6–10. Three patients required a blood transfusion of 1–2 pints. No nephrotoxicity, cardiotoxicity, hepatotoxicity were seen. Grade 1 neurotoxicity pre-existed in patients pre-treated with paclitaxel, but this neurotoxicity was not aggravated. None of the patients discontinued treatment due to drug-related toxicity Haematologic and non-haematologic toxicity is shown in Tables 3 and 4, respectively.

### Dose intensity

The patients received a total of 213 courses (median four courses per patient; range 2–6). Dose reduction after the first course of chemotherapy was necessary in three patients. The patients received 90% of the planned dose-intensity of each drug.

## Discussion

In the treatment of advanced breast cancer, the present study adds one more effective chemotherapy combination. When considering the fact that the majority of the patients were pre-treated (with two series of chemotherapy) and all patients had anthracyclines and the majority also had paclitaxel, a 52.08% (95% CI 37.95–66.21) response rate including three complete remissions (6.25%, 95% CI 0–13.05) is indicative of the high-calibre effectiveness of docetaxel combined with irinotecan. The addition of irinotecan seems to have contributed to this effectiveness. The combination of docetaxel and doxo-

**Table 3** Toxicity: haematological

| | Grade 3 | | Grade 4 | | Total | Percentage |
|---|---|---|---|---|---|---|
| | No. of patients | Percentage | No. of patients | Percentage | | |
| Neutropenia | 15 | 31.25 | 3[a] | 6.25 | 18 | 37.50 |
| Thrombopcytopenia | 3 | 6.25 | – | – | | |
| Anaemia | 14 | 29.17 | – | – | | |

[a]Febrile neutropenia in one (2.08%) patient

**Table 4** Toxicity: non-haematological

| | Grade 1 *n* (%) | Grade 2 *n* (%) | Grade 3 *n* (%) |
|---|---|---|---|
| Alopecia | – | 5 (10.42) | 43 (89.58) |
| Asthenia | 20 (41.67) | 8 (16.67) | – |
| Nausea/vomiting | 15 (31.25) | 2 (4.17) | – |
| Diarrhea | 9 (18.75) | 3 (6.25) | 1 (2.08) |
| Neuropathy | 30 (62.50) | 2 (4.17) | – |
| Cardiotoxicity | – | – | – |
| Nephrotoxicity | – | – | – |
| Hepatotoxicity | – | – | – |

rubicin has shown a better response and TTP, but no statistically significant difference in survival when compared with doxorubicin and cyclophosphamide given as a first-line treatment for metastatic breast cancer [1]. In the above study, the response rate was 59% with 10% CR (docetaxel and doxorubicin combination) which is comparable to the response in our study, despite the major difference: their treatment involved untreated patients while in ours, all patients had been pre-treated with agents including doxorubicin and taxanes. Patients in the other arm of the above study received doxorubicin and cyclophosphamide and the response rate was 47% (CR 7%). This result is not better than ours. The survival these authors report is superior to ours but this can be attributed to the fact that their patients had undergone no prior treatment, while our patients had been pre-treated. In another randomized study using doxorubicin and paclitaxel versus doxorubicin and 5-fluorouracil (5-FU) and cyclophosphamide as first-line chemotherapy in metastatic breast cancer, the responses were 68% and 55%, respectively, [26] a result superior to ours, although theirs was first-line treatment; these authors also reported the superiority of the doxorubicin-paclitaxel combination in TTP (8.3 months vs. 6.2 months, and of overall survival (23.3 months vs. 18.3 months, $P = 0.013$) TTP in our study was 8 months. A similar TTP (8 months) was also documented in another study where doxorubicin and paclitaxel were used as first-line treatment in metastatic breast cancer patients [29]. Results with high response rates but with similar TTP have been reported in other studies which used anthracyclines and/or paclitaxel as front-line treatment in advanced breast cancer patients [25, 30, 31].

A randomized trial [32] testing single administration of docetaxel 100 mg/m$^2$ versus docetaxel 75 mg/m$^2$ day 1, combined with capecitabine 1250 mg/m$^2$ twice daily, days 1–14, found that the response rate was superior to single docetaxel (42% vs. 30%). Median survival and TTP were also significantly superior. Another randomized trial [33] comparing the efficacy of paclitaxel versus paclitaxel combined with gemcitabine every 21 days reported that the combination provided significant overall survival advantage over paclitaxel. Recent data [34] in another randomized trial compared two schedules (paclitaxel combined with epirubicin versus paclitaxel combined with carboplatin) for median time to treatment failure and response rate. Although there was no significant difference in response rate, there was a statistically significant difference in the median duration of treatment failure, in favour of the paclitaxel-carboplatin combination.

A Phase II study [35] documented the combination of paclitaxel with carboplatin as first-line treatment in metastatic breast cancer patients. A 62% response rate was achieved in 53 patients (16% CR), median TTP was 7.3 months and 12-month survival 72%.

With respect to response rate and TTP, when we look at docetaxel used as a single agent in pre-treated patients, we find that the response rate was 30% and the TTP was 19 weeks, i.e. nearly 5 months [15]. Docetaxel has been shown to be highly active in patients with breast cancer; given as monotherapy in advanced breast cancer patients, a 37.5% complete and partial response rate was achieved with TTP at 23 weeks [36]. These results were confirmed in another trial [37] which tested single-agent docetaxel treatment in weekly and 3-weekly schedules in patients with advanced breast cancer, (including patients who had been pre-treated). Overall response was 34% and 33% in the weekly and 3-weekly schedules, respectively. Median time to progression was 5.7 in the weekly schedule and 5.3 months in the 3-weekly schedule.

The outcome our study's combination with a response rate of 52% and TTP of 8 months can be attributed to the addition of irinotecan to docetaxel.

An important contribution concerning the effectiveness of irinotecan was made in a trial [28] which used this agent as monotherapy. In patients with metastatic breast cancer, pre-treated and refractory to anthracyclines and taxanes, the 23% response rate and overall survival of 8.6 months are noteworthy.

The irinotecan-docetaxel combination was tested in biweekly administration as a phase I study [38] which included pre-treated patients with NSCLC and advanced-stage breast cancer. Toxicity was mainly diarrhea and neutropenia at doses of up to 80 mg/m$^2$ for docetaxel and 100 mg/m$^2$ for irinotecan. It is worth noting that the response rate was 51% (21/41 patients) and the major response was observed in the breast cancer patients (59%).

In conclusion, the combination of docetaxel and irinotecan produces a high response rate in pre-treated advanced breast cancer patients, comparable to other combinations that are used as first-line chemotherapy. The TTP is longer than that achieved by docetaxel monotherapy and it is also comparable to that of other first-line chemotherapy combinations.

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