Nonanthracycline Containing Docetaxel-Based Combinations in Metastatic Breast Cancer

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ABSTRACT
Many active nonanthracycline-containing regimens are emerging from clinical trials and may offer the option of treating metastatic breast cancer without resorting to doxorubicin or analogues. When used first-line in metastatic breast cancer, both cisplatin and carboplatin are active agents and hence candidates for combination therapy. In a dose-finding study in patients with no prior chemotherapy for metastatic disease, docetaxel administered together with cisplatin produced a promising response rate (RR) of 60% (73% in patients without prior adjuvant chemotherapy). The combination is feasible, although adequate hydration and antiemetic medication must be given. There is also an early indication that it may be possible to dramatically cytoreduce disease in patients with locally advanced breast cancer who are treated with docetaxel plus cisplatin. Given its lower toxicity, carboplatin may also have a role in combination with the taxanes. Of the nonplatinum agents, vinorelbine appears to hold promise; its combination with docetaxel produced an RR of 59% in a group of anthracycline-pre-treated patients with progressive disease. Forty-two percent of the patients studied also had prior exposure to a taxane. Weekly gemcitabine plus monthly docetaxel is feasible and active, as is the combination of docetaxel q 3 weeks with daily oral capecitabine. The Oncologist 2001;6(suppl 3):17-21

INTRODUCTION
Evidence to date suggests that docetaxel is one of the most active single agents in metastatic breast cancer [1, 2]. Docetaxel has been shown to be superior to doxorubicin in the treatment of patients with prior exposure to an alkylating agent-containing regimen, and it is also superior to mitomycin/vinblastine and methotrexate/5-fluourouracil (5-FU) in patients whose cancer had progressed following anthracycline therapy [3-6]. The latter finding is of particular relevance to designers of combination regimens in that it indicates at least a degree of non-cross-resistance between docetaxel and doxorubicin, and the use of these two drugs in combination thus seems logical. In two Breast Cancer International Research Group studies, docetaxel-doxorubicin combinations were superior to more traditional anthracycline-alkylating agent-based combinations. However, the increasing use of anthracyclines in the adjuvant setting mandates the development of nonanthracycline-containing, docetaxel-based combinations. Candidate drugs for such combinations include: vinorelbine, gemcitabine, cyclophosphamide, 5-FU, methotrexate, and mitomycin C.

Another group of agents which is seldom used in routine breast cancer clinical practice but which has been shown to have substantial activity in this disease are the platinum coordination complexes.

OVERVIEW OF PLATINUM AGENTS IN BREAST CANCER
Although cisplatin and carboplatin are seldom used in the routine treatment of breast cancer in the clinic, a critical look at the data suggests that these agents are among the most active drugs currently available for the initial treatment of metastatic breast cancer [7]. According to the review of Smith and Talbot, cisplatin can be expected to induce responses in around 50% of patients without prior chemotherapy [7], however the activity of these drugs in the salvage setting is much...
less prominent. Among 113 previously treated patients who were given cisplatin as second or subsequent treatment, the response rate (RR) was 9% (Table 1). While this appears to suggest a near-unique reduction in activity between first- and second-line use, at least a component of the reduction must be attributed to the fact that breast cancer patients given cisplatin in these trials had typically been exposed to a wide range of active agents including anthracycline.

Carboplatin also has activity in the first-line setting (Table 1) [7-16]. Four studies of the drug as initial chemotherapy reveal an overall RR of 31% (27 of 85 patients responded). In the second-line setting, the RR was 7% in four studies that included 60 cases. While these data might suggest that carboplatin is somewhat less active than cisplatin. The increasing understanding of the pharmacokinetics of carboplatin allows for the possibility that earlier studies which used body surface area might have been under-dosing.

**NONTAXANE, PLATINUM-CONTAINING COMBINATIONS**

The description of preclinical synergy between the platinum coordination complexes and etoposide has resulted in this combination being extensively tested in the clinic [17]. In a trial conducted by the North Central Cancer Treatment Group, cisplatin/VP-16 produced responses in 25% of pretreated patients [17]. Cocconi et al. randomized 140 previously untreated patients to receive either cisplatin/VP-16 or CMF [17]. The RR with cisplatin (63%) was statistically significantly superior to CMF (48%). Investigators at the Memorial Sloan-Kettering Cancer Center reported an RR of 42% in 19 patients with no prior cytotoxic exposure who were given carboplatin plus VP-16. However, the RR was only 8% among 12 patients with a history of adjuvant chemotherapy.

**PLATINUM/DOCETAXEL COMBINATIONS IN BREAST CANCER**

There has been considerable interest in combining docetaxel with platinum agents in ovarian and lung cancer. Much phase I work had therefore been completed in other disease areas. However, the combination of docetaxel with cisplatin has been studied in a phase I trial conducted in Ireland and France [18].

This study recruited patients with no prior chemotherapy for their metastatic disease. Patients had measurable and/or evaluable lesions, and a World Health Organization performance status of less than 2. A total of 72% of patients recruited to the dose-finding trial had received prior adjuvant therapy, and this had involved an anthracycline in 39% of cases. Many patients had relapsed within a year of adjuvant treatment.

Gastrointestinal (GI) toxicity was dose-limiting at amounts higher than 75 mg/m² of each drug (Table 2).

<table>
<thead>
<tr>
<th>Study</th>
<th>Prior chemotherapy</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolaric and Roth [8]</td>
<td>No</td>
<td>33/66 (50%)</td>
</tr>
<tr>
<td>Mechti and Sopova [7]</td>
<td>No</td>
<td>10/113 (9%)</td>
</tr>
<tr>
<td>Sledge [9]</td>
<td>No</td>
<td>7/75 (9%)</td>
</tr>
<tr>
<td>Yap [10]</td>
<td>Yes</td>
<td>4/60 (7%)</td>
</tr>
<tr>
<td>Ostrow [7]</td>
<td>Yes</td>
<td>4/60 (7%)</td>
</tr>
<tr>
<td>Forestier [7]</td>
<td>Yes</td>
<td>10/113 (9%)</td>
</tr>
<tr>
<td>Martino [11]</td>
<td>Yes</td>
<td>10/113 (9%)</td>
</tr>
<tr>
<td>Bajorin [12]</td>
<td>Yes</td>
<td>10/113 (9%)</td>
</tr>
</tbody>
</table>

Adapted with permission [7].

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Withdrawal prior to cycle 5 for toxicity (evaluable patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>85</td>
<td>75</td>
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<td>100</td>
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<tr>
<td>100</td>
<td>75</td>
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</tbody>
</table>

The combination of docetaxel with cisplatin in these first-line metastatic patients proved active, with an overall RR of 60%. In total, two complete responses (CR) were seen, and 16 partial responses (PR). Ten patients had stable disease, two progressive disease, and nine cases were not evaluable. Importantly, while the overall RR in all 30 evaluable patients was 60%, this rose to 73% in the subgroup of 15 patients with no prior adjuvant therapy.

In this study, adequate doses of antiemetics and hydration were both crucial. Nevertheless, the activity of the combination is promising, and it is recommended (given the GI toxicity at higher doses) that further work be undertaken using 75 mg/m² of both agents.

The combination of taxanes/platinum as chemotherapy for breast cancer has been studied by other investigators (Table 3). Gelmon et al. administered paclitaxel (90 mg/m²) and cisplatin (60 mg/m²) to 27 patients with prior anthracycline exposure, reporting an RR of 85% [19]. Higher dose paclitaxel (220 mg/m²) with cisplatin (75 mg/m²) produced...
The same RR was seen in a study in which 19 previously anthracycline-treated patients received docetaxel 75 mg/m² plus cisplatin 75 mg/m² [21]. Interestingly, a similar regimen (75 mg/m² docetaxel plus 80 mg/m² cisplatin) produced a 56% RR in 41 patients with anthracycline-resistant disease [22]. Also in a resistant population, Antoine et al. found a 52% RR in 65 patients given docetaxel 100 mg/m² plus cisplatin 100 mg/m² [23].

Investigators in Miami have reported striking results with docetaxel/cisplatin in patients with stage III breast cancer [24]. The overall RR was 96% (CR 52%; PR 44%).

In a trial involving docetaxel, administered at 75 mg/m², carboplatin was given to an area under the concentration time curve of 5 [25]. The RR in 20 second-line patients was 40%. A similar RR (44%) was seen when paclitaxel was combined with carboplatin, again in anthracycline-resistant patients (Table 4) [26].

**DOCETAXEL PLUS VINORELBINE**

In a Southwest Oncology Group phase II study, docetaxel was administered together with vinorelbine (and G-CSF support) to a group of patients with poor-prognosis stage IV breast cancer [27]. Patients entered had progressed while receiving an anthracycline or relapsed within a year of such therapy. Prior paclitaxel treatment was allowed.

Docetaxel was administered at 60 mg/m² on day 1 and vinorelbine 27.5 mg/m² on days 8 and 15, q 3 weeks. G-CSF was administered on days 2-21 of each cycle in all patients. The 13% of patients who were HER-2-positive also received Herceptin.

Of the 36 patients entered, 84% had visceral disease. The median number of disease sites was two and median number of prior treatment regimens 1.8. Forty-five percent of patients had already been exposed to a taxane.

The overall RR in this group of patients with extensive disease and pretreatment was 59%: 10 patients had a CR and 9 a PR. The median time to progression was 10 months.

**DOCETAXEL PLUS GEMCITABINE**

Laufman et al. studied a regimen of weekly gemcitabine plus monthly docetaxel in the therapy of patients with metastatic breast cancer [28]. This phase II study followed previous work showing that weekly gemcitabine could safely be combined with docetaxel and that four of the seven poor-risk patients treated had a response [29].

In the phase II trial, gemcitabine was given at 800 mg/m² on days 1, 8, and 15 while docetaxel was administered at 100 mg/m² on day 1, q 4 weeks [29]. Response was assessed after the second and fourth cycles, and responding patients had the option to continue treatment. Based on intent-to-treat, the RR was 79% among 39 patients (there were 2 CRs and 29 PRs; three patients each had stable and progressive disease, and two were lost to follow-up). The median response duration among patients who responded to this regimen given as first-line treatment for metastases was more than 26 months. One- and two-year survival rates were 74% and 65%, respectively. Patients for whom the gemcitabine/docetaxel combination was second-line therapy for metastatic disease had a median survival of 10 months and 44% were alive at 1 year.
In a phase I study, docetaxel 75, 85, or 100 mg/m² was administered on day 1 q 3 weeks with capecitabine (given orally bid at doses of 825, 1,000, or 1,250 mg/m² on days 1-14) [30]. The 33 patients treated in this dose-escalation trial had solid tumors that had not responded to standard therapy, and a Karnofsky performance score of 70 or greater.

The dose-limiting toxicities were grade 2/3 asthenia, grade 3 septicemia, and grade 3 nausea. Two of three patients had solid tumors that had not responded to standard therapy, orally bid at doses of 825, 1,000, or 1,250 mg/m² on days 1-14) [30]. The 33 patients treated in this dose-escalation trial had solid tumors that had not responded to standard therapy, and a Karnofsky performance score of 70 or greater.

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In a phase III study in which recruitment is now complete, patients with metastatic breast cancer who had failed anthracycline therapy were randomized to receive either docetaxel 100 mg/m² q 3 weeks or 75 mg/m² docetaxel plus capecitabine 1,250 mg/m² administered bid on days 1-14 of each cycle. The primary objective of the study is to demonstrate superior time to progression in the combination arm. Results are awaited.

## DISCUSSION

Platinums are active agents in breast cancer [24]. The demonstrations of substantial activity for the combination of docetaxel and cisplatin are particularly interesting, given the proven synergy between these drugs and trastuzumab.

However, the early use in metastatic breast cancer of combinations of highly active drugs raises difficult questions about the sequencing of therapy. Might we be doing patients a disservice by using up too many of our therapeutic options at once? Such issues can only be resolved by carefully designed and conducted randomized trials. Meanwhile, the exceptionally high RR recorded by combination therapy (especially taxane/anthracycline combinations) must be considered encouraging. Furthermore, patients who have had such therapy early in the treatment history of their metastatic disease retain the possibility of having other active regimens, such as those based on weekly docetaxel, vinorelbine/5-FU, and capecitabine, on relapse.


