Salvage Chemotherapy for Metastatic Breast Cancer

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Introduction

Chemotherapy for metastatic breast cancer patients was widely adopted in the 1970s. Since then, clinicians have learned that (1) chemotherapy improves survival by nine to 10 months, on average, (2) the primary goal of treatment is disease palliation, (3) response to therapy is generally associated with a reduction in tumor-related symptoms, and (4) anthracyclines and taxanes are the most active agents. Despite these accepted realities, it is helpful to retain a certain humility in the face of the complex biology and heterogeneity that characterize this disease.

Survival After First Relapse of Breast Cancer

Disease-free interval from primary cancer diagnosis, estrogen-receptor status, and dominant site of metastases are factors associated with the widely varying survival rates following the first relapse of breast cancer. In one review, Vogel et al.² found that median survivals after first relapse range from less than two years to almost four years (Table 1). (Please see printed copy.)

Recent clinical trial experience has added hope to the goal of extending survival in primary breast cancer patients at high risk for relapse. A CALGB study³ demonstrated that adjuvant paclitaxel reduced the odds of recurrence and death by 22% and 26%, respectively, when it was introduced in node-positive breast cancer patients following four cycles of AC. Based on these data, an increasing proportion of women will likely receive both anthracyclines and taxanes in the adjuvant setting.

Treatment After Anthracycline and Paclitaxel

Salvage chemotherapy in patients whose disease has progressed with both anthracyclines and taxanes is a less studied approach. The scope of experience in these patients and the associated response rates are shown in Table 2.⁴–⁹ In addition to these chemotherapeutics, in which response ranged from 0% to 27%, trastuzumab produced a response rate of approximately 16% in a cohort in which 68% of patients had been treated and had failed anthracyclines and paclitaxel.¹⁰ The recent introduction of the oral fluoropyrimidines for the treatment of patients with metastatic breast cancer has provided new data and a new treatment alternative.

Table 2. — Treatment After Anthracycline and Paclitaxel

<table>
<thead>
<tr>
<th>Drug</th>
<th>Population</th>
<th>Number of Patients</th>
<th>Response Rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Paclitaxel resistant, exposed to anthracycline</td>
<td>36</td>
<td>18%</td>
<td>Valero et al.⁴</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Paclitaxel failures, 71% exposed to anthracycline</td>
<td>14</td>
<td>0%</td>
<td>Fazeny et al.⁵</td>
</tr>
<tr>
<td>Vinorelbine + G-CSF</td>
<td>95% paclitaxel refractory, 100% exposed to anthracycline</td>
<td>40</td>
<td>25% (ITT)</td>
<td>Livingston et al.⁶</td>
</tr>
<tr>
<td>Paclitaxel (96 hrs)</td>
<td>Disease progression on taxanes, 33% exposed to anthracycline</td>
<td>28</td>
<td>27% (7/26)</td>
<td>Seidman et al.⁷</td>
</tr>
<tr>
<td>5-Fluorouracil (CI)</td>
<td>Prior anthracycline paclitaxel and/or paclitaxel</td>
<td>35</td>
<td>12% (ITT)</td>
<td>Ragaz et al.⁸</td>
</tr>
<tr>
<td>Weekly paclitaxel</td>
<td>Failed q 3 weekly taxane</td>
<td>50</td>
<td>20%</td>
<td>Perez et al.⁹</td>
</tr>
</tbody>
</table>

ITT = intent to treat
CI = continuous infusion
G-CSF = granulocyte colony-stimulating factor

Taxanes (Paclitaxel and Docetaxel)

At the 1999 meeting of the American Society of Clinical Oncology (ASCO), Fornier et al.¹¹ presented results of a phase II trial with weekly trastuzumab plus 1 hour paclitaxel (90 mg/m²) in metastatic breast cancer patients who were HER2 overexpressers or HER2 non-overexpressers. In 17% of the patients, taxane therapy had been prescribed more than one year prior (the median dose intensity of paclitaxel was 82 mg/m²). The overall response rate was 53%: 62% in the HER2 overexpressers, and 44% in the HER2 non-overexpressers. Dose-limiting toxicity was peripheral neuropathy. One episode of congestive heart failure occurred in a patient who had received a total dose of 615 mg/m² of doxorubicin four weeks prior to beginning therapy with paclitaxel and Herceptin (trastuzumab). Most patients developed alopecia from this regimen, although it generally is active and tolerable in patients who have failed prior chemotherapy.

The efficacy and safety of weekly docetaxel for metastatic breast cancer patients were examined in a study from Löfler and colleagues.¹² The regimen consisted of approximately 30 mg/m² per week escalating up to 45 mg/m² per week given over 15 to 30 minutes for six weeks, followed by a two-week rest. Of 31 patients who had received one to three prior chemotherapy regimens, 26 were evaluable. The response rate was 50% (16% complete response and 35% partial response). Adverse events were mild leukopenia and
Another phase II study\textsuperscript{13} of weekly docetaxel involved 29 patients who received doses of 40 mg/m\textsuperscript{2} (median dose intensity was 29 mg/m\textsuperscript{2} per week). A 41% response rate was achieved. Fourteen percent of the patients had stable disease for six months of more, and 41% developed grade 2 alopecia. Based on these and other trials in the setting of metastatic breast cancer, docetaxel is an active salvage regimen for patients who have received prior anthracycline therapy.

In a study that demonstrated longer survival,\textsuperscript{14} do cetaxel alone was compared to mitomycin C plus vinblastine in patients whose disease was resistant to an anthracycline. This randomized trial of 392 patients showed a 30% response rate with docetaxel and an 11.5% response rate with mitomycin C plus vinblastine. Median survival was 11.4 months for the docetaxel arm and 8.7 months for the mitomycin C plus vinblastine arm.

**Capcitabine**

Capcitabine is an orally active fluoropyrimidine carbamate that is converted by a series of three enzymatic reactions to 5-fluorouracil (5FU). The final enzymatic step is catalyzed by thymidine phosphorylase, which is overexpressed in a number of human cancers (breast, cervical, colorectal, and stomach), allowing capcitabine to be finally converted to 5FU at the tumor site.

In a pivotal, open-label, multinational phase II study\textsuperscript{15,16} involving 25 centers, patients with metastatic breast cancer resistant to paclitaxel received 2,500 mg/m\textsuperscript{2} of oral capcitabine per day, divided into two doses, using a schedule of two weeks on the drug followed by a one-week rest period. This regimen was repeated in three-week cycles (Table 3). Of 162 patients receiving capcitabine, 135 had measurable disease and 27 had evaluable disease. Sixty-eight percent of patients had more than two metastatic sites; 75% of these patients had predominantly visceral disease, 22% had predominantly soft-tissue disease, and 3% had predominantly bone disease. Approximately 40% of patients received capcitabine as third-line therapy, and 40% received the agent as fourth-line therapy.

**Table 3. Multicenter Phase II Studies of Capcitabine in Paclitaxel/Taxane-Refractory Metastatic Breast Cancer**

<table>
<thead>
<tr>
<th>Dose/Regimen</th>
<th>Enrolled</th>
<th>Median Duration of Response</th>
<th>Median Survival</th>
<th>Time to Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capcitabine in Paclitaxel-Refractory Metastatic Breast Cancer\textsuperscript{15}</td>
<td>162</td>
<td>9.1 mos</td>
<td>2.8 mos</td>
<td>93 days</td>
</tr>
<tr>
<td>Capcitabine in Taxane-Refractory Metastatic Breast Cancer\textsuperscript{16}</td>
<td>74</td>
<td>8 mos</td>
<td>Not yet available</td>
<td>3.7 mos</td>
</tr>
</tbody>
</table>

The overall response rate was 20% (95% confidence interval, 14% to 28%), and an additional 40% of patients had stable disease for a median of 3.5 months. The median duration of response was 241 days. Median overall survival was 12.8 months, and one-year survival was 52%. In the 42 patients who were refractory to both doxorubicin and paclitaxel (disease had progressed on therapy), the response rate associated with capcitabine was 29%.

The most common treatment-related adverse events associated with capcitabine therapy were hand-foot syndrome, diarrhea, stomatitis, and fatigue. Adverse events occurring at grade 3 or 4 levels were diarrhea (11% were grade 3, 3% were grade 4), hand-foot syndrome (10% were grade 3), and stomatitis (7% were grade 3). There were no treatment-related deaths. Overall, 4% of patients experienced grade 4 adverse events, 7% withdrew due to adverse events, and 10% were hospitalized due to treatment-related events. The authors concluded from this trial that capcitabine is an active agent in the treatment of paclitaxel-refractory metastatic breast cancer.

In a 1999 ASCO poster, Blum et al\textsuperscript{16} presented results from another capcitabine study in taxane-refractory metastatic breast cancer patients. Seventy-four patients who were pretreated with at least two chemotherapy regimens, including paclitaxel or docetaxel, demonstrated a response rate of 24% (Table 3) with capcitabine therapy. The median duration of response was eight months; time to progression was 3.7 months. Using the visual analogue scale (VAS), 27% of patients had significant improvement in their pain. Diarrhea (18%), hand-foot syndrome (18%), and nausea (11%) were the only treatment-related adverse events to occur at grade 3 or 4 levels in more than 10% of patients.

**Vinorelbine**

Based on data from approximately eight prior trials, single-agent vinorelbine has significant activity in metastatic breast cancer, especially in minimally pretreated patients.\textsuperscript{17} In a phase II study with 145 evaluable patients who had not received prior chemotherapy, vinorelbine was associated with a 42% response rate.\textsuperscript{17} As expected, response rates decreased with extent of pretreatment: a large multicenter study showed a 16% response rate in patients treated with one to two prior chemotherapy regimens.\textsuperscript{17} Livingston et al\textsuperscript{6} demonstrated a response rate of 25% with dose-intensive weekly vinorelbine (35 mg/m\textsuperscript{2}) in combination with granulocyte-colony stimulating factor (G-CSF) in patients who had been pretreated with an anthracycline and paclitaxel.
Gemcitabine

Gemcitabine, a new agent with a novel mechanism of action affecting pyrimidine synthesis and inhibition of ribonucleotide reductase, has demonstrated efficacy in a variety of solid tumors, including metastatic breast cancer. Three phase II studies are notable. Carmichael et al18 and Spielman et al19 investigated the agent in patients who had failed one prior regimen and demonstrated response rates of 25% to 28%, respectively. In patients who had received only prior adjuvant chemotherapy, Blackstein and colleagues20 demonstrated a response rate of 37% (95% CI: 23% to 57%). Interestingly, the median duration of response was robust in these studies, at approximately 12 to 13 months. Larger phase II studies of gemcitabine are needed to further define its efficacy in metastatic breast cancer. Like vinorelbine and capcitabine, gemcitabine is not associated with alopecia, a feature worthy of consideration in the hierarchy of benefits for patients.

Multitargeted Antifolate

Multitargeted antifolate (MTA), a broad-spectrum antifolate, inhibits three different enzymes that utilize folates. Preliminary results from phase I studies point to potential activity in patients with colorectal, breast, and head and neck cancers, mesothelioma, and non-small cell lung cancer. Martin et al21 conducted a study of MTA as an intravenous infusion of 600 mg/m² every 21 days in 64 patients with advanced breast cancer who had progressed after anthracycline treatment. An overall response rate of 23% was achieved, with no difference for patients whose disease had progressed while receiving an anthracycline compared to those whose disease progressed more than 30 days after stopping the anthracycline. Toxicities included moderate neutropenia, nausea, vomiting, and skin rash.

The efficacy of sequential combinations vs sequential single agents in metastatic breast cancer represents an area of ongoing study. One randomized trial that addressed this important issue was conducted by investigators in Finland and published in 1998.22 Approximately 300 metastatic breast cancer patients were randomized to two treatment arms — either sequential combination or sequential single-agent therapy. The combination chemotherapy arm consisted of CEF as front-line therapy (500 mg/m² of cyclophosphamide on day 1, 60 mg/m² of epirubicin on day 1, and 500 mg/m² of 5FU on day 1 to next cycle day 22). Single-agent epirubicin as front-line therapy consisted of 20 mg/m² weekly. At the time of disease progression, patients who had been previously treated with CEF received another combination — in this case, 8 mg/m² of mitomycin C and 6 mg/m² of vinblastine. Patients who had been previously treated with single-agent epirubicin received single-agent mitomycin C (8 mg/m²/day). As expected, the response rates for the first-line combination were higher with CEF than with weekly epirubicin (53% vs 44%, respectively). No difference in stable disease rates was found between the groups. Second-line response rates for mitomycin C and vinblastine were 6% vs 14% for mitomycin C. The observed improvement in progression-free survival with the combination was transient and not statistically significant. The finding of no difference in overall survival is in agreement with the ECOG study by Sledge et al that compared single-agent doxorubicin vs single-agent paclitaxel vs the combination. Survival was equivalent among all three approaches.23

Conclusions

These and other studies in metastatic breast cancer show that regimens or agents with low levels of activity in metastatic breast cancer tend to result in inferior survival compared with agents that have excellent single-agent activity. However, it does not appear that increasing response rates with combinations beyond some threshold level further improves survival of patients with metastatic breast cancer.

An effective overall approach to treating and caring for most advanced breast cancer patients (those without visceral crisis) might be described as a chronic disease model — using effective sequential single agents, focusing on the patient’s duration and quality of life, and striving to control disease, maintain performance status, and minimize toxicity and inconvenience.

References

Discussion

Dr Horton: The variety of treatments available for patients who need salvage chemotherapy can be confusing to patients and physicians. What are your thoughts from your own practice for choosing a salvage program for patients who are resistant to both anthracycline and the taxanes?

Dr O'Shaughnessy: I always enroll a patient on a phase II or III study if one is available. In the absence of a trial for which the patient is eligible, I turn to capecitabine, mainly because that is where we have data. I can tell the patient what her chances of responding are, including those with visceral and liver disease. If the patient had not had trastuzumab, then this is another option if her disease overexpresses HER2. Gemcitabine and navelbine are not cross-resistant with anthracyclines, so I believe these are other reasonable agents. While we do not yet have substantial data to guide us beyond that point, we do have a number of different therapies, particularly for patients whose disease has responded to chemotherapy. For patients with refractory breast cancer (to two or three agents), I believe it's reasonable to stop chemotherapy.

Dr Perez: I think we are going to discover that the response rates are approximately the same with capecitabine or with weekly paclitaxel after disease progression on taxane therapy administered every three weeks. I believe weekly paclitaxel would have to be considered as potential third-line therapy for patients with metastatic breast cancer. For now, until we have the data, my choices have been to use capecitabine or trastuzumab for patients with HER2 overexpression.

Dr Muss: If patients have been adequately treated with taxanes and anthracyclines, capecitabine is an excellent drug. Also, I think trastuzumab is a quality of life drug — it is well tolerated, does not cause hair loss, and has very little myelosuppression. Likewise, gemcitabine, though not approved by the FDA, is not unreasonable, and neither is vinorelbine. However, the problem is returning to weekly intravenous therapy with chemo therapy, which is inconvenient for patients. Therefore, I think it is beneficial to have an oral agent to use.

Dr Sledge: My guess is that if you were to poll a wide variety of physicians, you would find some who like to use capecitabine, some who like to use vinorelbine, and some who like to use gemcitabine. It is unlikely that we will ever have any phase III trials large enough and meaningful enough to tell us that drug A is better than drug B for this particular patient. In fact, all of our therapy is somewhat mediocre as third-line treatment for metastatic breast cancer.

Dr Horton: I can understand your saying that the results of the treatments are mediocre, and that may be true when looking at populations of patients who have been treated. But certainly, for individuals, you can obtain marked and extremely useful clinical results.

Dr Sledge: I don't disagree with that for the individual. The problem, of course, is that we don't know in advance who is going to benefit. I think it would be equally reasonable to ask the patient who experiences appreciable treatment-related side effects followed by progressive disease three weeks later whether she felt she had benefited from that particular therapy. The question is not so much whether an individual will benefit, because individuals always benefit with some therapies. The question is rather whether we are improving the sum total of human happiness with third-line therapy for metastatic disease.

Dr Slamon: I think we would do well to disseminate information to clinicians that, for a patient who has failed first-line treatments and has metastatic disease, there is an equivalent landscape of five or six different drugs or schedules and that the appropriate place for receiving treatment is within a clinical trial.

Dr Horton: It's easy to say that we should put more patients on clinical trials, but the trials have to hold the promise of doing something considerably better than what we have available at the present time. And I'm not sure I see these things on the horizon yet.

Dr Sledge: When using capecitabine, do you prescribe the registration dose or a lower dose?

Dr O'Shaughnessy: This drug was approved at its maximal tolerated dose. However, I start capecitabine at 75% of this dose for patients who have significant liver involvement and abnormal liver function. There is a significant increase in the AUC of both capecitabine and 5FU in this situation. Another special consideration is the elderly. In the pivotal study, women over 80 years of age had an unacceptable rate...
of grade 3 or 4 toxicity. I decrease the dose to 75% for these patients or for frail patients in their 70s. The third consideration is performance status. I have successfully used this drug in patients with an ECOG performance status of 3 or 4 who have massive liver disease and who had never had a fluoropyrimidine. I start its use at approximately 75%. Food is an important consideration as well. All of the studies administered capecitabine after breakfast and after dinner because food decreases the absorption and the AUC. So if women are not eating very well, they may absorb more drug and experience more toxicity. In the pivotal study, the patients who required a 25% dose reduction had no difference in response rate compared to those who received full dose, and they did not lose a response that had begun at full dose.

Approximately one third of patients require a second dose reduction down to 50% of the full dose. If I attempt to give the 50% dose continuously without a break, they usually do not tolerate it. I have also found that with the one week off, some will lose their responses at the 50% dose level. I think schedules with this drug can be explored, such as five days on and two days off, etc. Capecitabine generally works clinically to improve symptoms fairly quickly — within a couple of weeks — and significant toxicity can be avoided by educating patients to hold the drug for grade 2 diarrhea or hand-foot syndrome.

Dr Horton: With those kinds of dose reductions, how severe a problem is, for example, hand-foot syndrome?

Dr O'Shaughnessy: In the early experience with this drug, about 3% of patients had significant problems such as blistering, moist desquamation, etc. However, in my experience, the more common scenario is the patient with some diabetes and a little peripheral neuropathy, and she cannot walk without significant pain for a day or two if she gets grade 3 hand-foot syndrome. There is no peeling or desquamation, but it can be painful to walk. This is rapidly reversible; if we just hold the drug, it will reverse within a day or two. However, I instruct women not to get to this point and ask them to hold the drug and call me if their hands or feet start to hurt.

Dr Sledge: Do we have any better understanding now of what causes the hand-foot syndrome? Is there another approach than simply holding the dose that will allow us to ameliorate this?

Dr O'Shaughnessy: Let me answer the latter question first. There is really nothing good to treat it. I think prevention is the goal. Some have tried pyridoxine, vitamin B6, at 150 to 300 mg. I have also heard that the full complement of B vitamins can be somewhat helpful. Both are strictly anecdotal reports. Very thick emollients help symptomatically to some extent.

We do not know why it occurs. I suspect it is the buildup of drug or 5FU metabolites in the skin.

Dr Slamon: One of the fascinating things about breast cancer is that in recent years, we pretty much dropped fluorouracil in the adjuvant setting without any randomized trials whatsoever to indicate that AC was even equivalent to FAC or CAF. In fact, there was some inferential data that it might be inferior. With capecitabine coming in, are studies being performed that will explore moving capecitabine into a more front-line or adjuvant setting?

Dr O'Shaughnessy: There are impressive data showing synergy in preclinical models among paclitaxel, docetaxel, capecitabine — to a greater extent than with 5FU. Those combinations are being explored now in phase II and III studies. A large study is exploring docetaxel plus capecitabine vs docetaxel alone. Also, the weekly taxanes with capecitabine are being investigated, which are interesting, thinking ahead to the adjuvant setting. These regimens may also help us if we want to introduce trastuzumab, for example, into some of the adjuvant therapies.

Dr Horton: Do you have any additional data on specific studies that have been planned for gemcitabine?

Dr O'Shaughnessy: One of our goals is to improve on the AC followed by a paclitaxel adjuvant regimen. We're developing the paclitaxel/gemcitabine doublet to take advantage of this well-tolerated and active combination. Ross Donehower at Johns Hopkins is now developing the weekly paclitaxel/gemcitabine regimen for phase II testing. Also, we plan and hope to study weekly paclitaxel and gemcitabine, plus or minus trastuzumab.