First-line chemotherapy for metastatic breast cancer has been the focus of ongoing controversy, a condition that partially reflects the imperfections of available therapy. It also partially reflects not only the imperfections in our ability to monitor response, but also the disagreements among clinicians over the goals of therapy. Each physician maintains a hierarchy of goals for the treatment of patients—prolongation of survival, palliation of symptoms, minimization of toxicity, and rarely, in a small fraction of patients, the potential for cure.

Available Agents

Single Agents

The first principle of chemotherapeutics for metastatic disease is to begin therapy with single agents having a demonstrated efficacy as first-line therapy. Fortunately, a large number of such agents are available to patients and their physicians: anthracyclines such as doxorubicin, alkylating agents such as cyclophosphamide, antimetabolites such as fluorouracil and methotrexate, and microtubule inhibitors such as the taxanes and vinorelbine. Response rates for these agents range from mid 20% to high 60% (Table 1).

Combination Therapy

Combinations of agents have been used since the 1960s, when Ezra Greenspan\(^1\) published his work describing the potential of drug combinations to increase cell kill and possibly improve response in breast cancer patients. Today, while combination therapy has yielded better response rates, important questions remain as to whether it is superior to single-agent sequential therapy, especially in light of therapeutic goals other than response, such as longer survival. In previously untreated patients, standard combinations are typically associated with response rates of about 60%, with CR occurring in 10% to 20% of patients. Median durations of response are only in the six- to 12-month range, and both rates are reduced in metastatic patients who have had prior adjuvant chemotherapy.

Anthracycline vs CMF Combinations

To address the question of whether one regimen is better than another, A'Hern and colleagues\(^2\) conducted a meta-analysis of trials in which doxorubicin was substituted for methotrexate in a randomized setting. This study showed an overall 44% increase in the response rate for patients receiving an anthracycline, generally doxorubicin, in place of methotrexate. Anthracycline-treated patients had a 31% reduction in the hazard of treatment failure and a 22% reduction in the hazard of dying (\(P<0.001\)).

A recent overview of randomized literature evaluating first-line chemotherapy for metastatic disease is summarized in Table 2.\(^3\) The authors found that, first, polychemotherapy (PCT), or standard combination chemotherapy yields a higher overall response rate on average than monochemotherapy (MCT). There was a slightly higher overall response rate with anthracycline-based therapy vs non-anthracycline therapy. In this study, there were only slight differences among other types of chemotherapy, non-anthracycline-based chemotherapy, and CMF (cyclophosphamide, methotrexate, and 5-fluorouracil). In a comparison of high-intensity vs low-intensity therapy, a small benefit was seen in favor of high-intensity dose, as measured by response rate.

### Table 1.— Single-Agent Chemotherapy in First-Line Treatment of Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>ORR (%) (mean)</th>
<th>Drug</th>
<th>ORR (%) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>43</td>
<td>Paclitaxel</td>
<td>36-62</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>36</td>
<td>Docetaxel</td>
<td>52-68</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>28</td>
<td>Vinorelbine</td>
<td>40-52</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ORR = objective response rate

### Table 2.— Metastatic Breast Cancer: Overview of Chemotherapy

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Response</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% PR</td>
<td>95% CI</td>
</tr>
<tr>
<td>PCT vs MCT</td>
<td>48 vs 34</td>
<td>1.73</td>
</tr>
<tr>
<td>A vs Non-A</td>
<td>51 vs 45</td>
<td>1.39</td>
</tr>
<tr>
<td>Other CT vs CMF</td>
<td>49 vs 44</td>
<td>1.22</td>
</tr>
</tbody>
</table>
Survival Following FAC

Investigators at M.D. Anderson evaluated the survival impact of a doxorubicin-based combination chemotherapy in patients with metastatic breast cancer. Although utilizing nonrandomized, retrospective data, this series involved a large number of patients and represented an impressive analysis. The results suggested that there is a small but definite fraction of patients who are cured with combination chemotherapy. In this study, 1,581 patients received doxorubicin-containing chemotherapy (usually an FAC-type chemotherapy) between 1973 and 1982. CRs occurred in 263 patients (16.6%). Of these, 49 patients, or 3.1% of the overall CR group, maintained their remissions for five years or more. Twenty-six of the 49 CR patients were still alive and disease-free after a median of 191 months of follow-up (range: 135 to 254 months).

Who are the long-term survivors among patients who get chemotherapy for metastatic breast cancer? Based on the M.D. Anderson experience, younger women are more likely to be complete responders of greater than five years' duration (median age: 47 for CRs vs 54 for all patients), as are patients with a good performance status (63% of CRs vs 32% of all patients). Patients with a relatively low tumor burden were more frequently long-term complete responders. Finally, patients with only one or two metastatic sites were more likely to be alive and disease-free five or more years from initiation of therapy — one site: 55% of CRs vs 29% of all patients; two sites: 92% of CRs vs 62% of all patients.

Statxanes

In recent years, there has been an explosion in new agents for the treatment of breast cancer. The taxanes have dominated the therapeutic scene over the past decade. While phase II trials of taxanes suggested response rates in the 50% to 60% range, phase III trials have indicated a lower level of response.

In an ECOG trial (E-1193), my colleagues and I compared single-agent doxorubicin to single-agent paclitaxel to the combination of doxorubicin and paclitaxel in patients receiving front-line chemotherapy for metastatic disease (Table 3). Our findings confirmed the results of other investigators that single-agent taxanes perform within the same general overall range as single-agent anthracyclines, that the combination of both generates a statistically significant improvement in response rates, and that the taxanes have a statistically significant effect on time to treatment failure without affecting overall survival or quality of life. Nevertheless, they don't affect overall survival when given in the front-line setting. Median survivals for all three arms were not only equivalent to each other, but also largely equivalent to virtually every other trial of the past two decades for patients with metastatic breast cancer.

Table 3.— A Phase III Study (ECOG 1193) of Doxorubicin and Paclitaxel in Metastatic Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Doxorubicin*</th>
<th>Paclitaxel**</th>
<th>Doxorubicin + Paclitaxel***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>36%</td>
<td>34%</td>
<td>47%*</td>
</tr>
<tr>
<td>Complete Response</td>
<td>6%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Time to Treatment Failure (mos)</td>
<td>5.9</td>
<td>6.0</td>
<td>8.0*</td>
</tr>
<tr>
<td>Median LVEF Change</td>
<td>-10.5%</td>
<td>-3.0%</td>
<td>-7.0%</td>
</tr>
<tr>
<td>Maximum Doxorubicin Dose</td>
<td>480 mg/m²</td>
<td>480 mg/m²</td>
<td>400 mg/m²</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>9%</td>
<td>4%</td>
<td>9%</td>
</tr>
</tbody>
</table>
| LVEF = left ventricular ejection factor
  * 60 mg/m² doxorubicin
  ** 175 mg/m² paclitaxel 24 hrs
  *** 50 mg/m² doxorubicin; 4 hrs later 150 mg/m² paclitaxel 24 hrs + G-CSF


This outcome raises an important question. The central dogma of chemotherapy for metastatic breast cancer, which dates back over the past two decades, has been that combined chemotherapy agents will produce maximum benefit for patients. However, based on our findings and the results of a number of other recent trials, there is little good evidence to suggest that combination therapy is superior to sequential single-agent therapy.

Dose Intensity and High-Dose Therapy

Potentially fruitful avenues of research involving the taxanes are new dosing and administration schedules. These studies are based in part on a pharmacokinetic rationale that argues that weekly therapy using relatively low doses of paclitaxel or docetaxel can achieve a
peak plasma concentration and time above the therapeutic threshold well within the range of bolus therapy given at higher doses on an every-three-week basis. From a pharmacodynamic standpoint, weekly taxane administration offers the possibility of continuous exposure at the tissue level, where drug binding is avid. In addition, the taxanes may also be active antiangiogenic agents.

A number of weekly taxane regimens have been studied. One example from the Sloan-Kettering Group used weekly intravenous doses between 80 and 100 mg/m² given over one hour. The investigators reported an overall 53% response rate in their patients, many of whom had received prior chemotherapy regimens. Perez et al. reported an approximately 20% rate using a dose of 80 mg/m² per week, and Sikov et al. administered paclitaxel intravenously over three hours in doses up to 175 mg/m² weekly for six of eight weeks. Another group in Dortmund, Germany, gave docetaxel at doses ranging between 30 and 45 mg/m² over one hour, weekly, for six of eight weeks. The Sikov study showed an overall response rate of 78% in 18 patients as frontline therapy, with a rare occurrence of febrile neutropenia. The Dortmund study, looking at a more heavily pretreated group, showed a 40% response rate and no febrile neutropenia.

Dose intensity is an area of great interest to many investigators. In the early 1980s, Hryniuk and Bush presented a dose intensity hypothesis that has been applied to many diseases but was first applied to metastatic breast cancer. When this hypothesis is applied to an analysis of almost 20 prospective, randomized trials, it is apparent that an improvement in overall survival with increases in dose intensity did not occur in the majority of trials.

Researchers have also studied very high-dose chemotherapy in patients with metastatic breast cancer, based on a number of phase I and II trials. Selection bias is a problem with some phase II trials, and it may inhibit its extrapolation to the larger universe of patients.

The group at M.D. Anderson looked at the issue of patient selection in metastatic breast cancer. Their purpose was to determine survival with doxorubicin-based metastatic therapy based on high-dose chemotherapy selection criteria. The selection criteria were age less than 60 years, relatively good performance status, CR or PR to chemotherapy, normal liver function, good marrow function, and no symptomatic cardiac dysfunction. Overall survival for patients who would have been candidates for bone marrow transplantation but who received standard doxorubicin-based chemotherapy was about 30 months, compared with 17 months for noncandidates (Pc.001). Progression-free survival was nearly twice as long in candidates for transplant vs noncandidates — 16 months vs eight months, respectively (Pc.001). The data strongly suggest that selection bias can explain some of the results in phase II and phase III trials of high-dose therapy for metastatic disease.

The obvious solution to this problem is to look at high-dose chemotherapy in transplantation in the phase III setting. Bezwoda in Johannesburg enrolled women under 50 years of age previously untreated metastatic breast cancer. Subjects were randomized to receive either cyclophosphamide, mitoxantrone, and vincristine for six to eight cycles of high-dose chemotherapy with cyclophosphamide, mitoxantrone, and etoposide (CNV), with stem cell support for two treatments. Patients in this trial who received high-dose chemotherapy had the strikingly high CR of 51% (vs 4% for CNV). They also had statistically significant improvements in duration of response (80 weeks for high-dose patients vs 34 weeks for CNV patients) and overall survival (90 weeks for high-dose patients vs 45 weeks for CNV patients). This trial had only about 90 patients, raising the possibility that the results might represent a statistical artifact.

The "Philadelphia" Intergroup Study (PBT-1) trial opened in 1990 and randomized between high-dose chemotherapy (HDC) and stem cell support (SCT) vs maintenance chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) for women with metastatic breast cancer who are responding to conventional induction chemotherapy. A total of 553 with a median age of 45 years received four to six cycles of CAF or CMF. Patients were then randomized to either receive high-dose chemotherapy with the STAMP-V regimen and stem cell support or receive maintenance chemotherapy with CMF for two years. There was no difference in survival or severe toxicity between patients on the high-dose chemotherapy arm and patients on the CMF maintenance arm. Based on the results of this trial, especially given the relatively large number of patients, it is apparent that high-dose chemotherapy has no established role for patients with metastatic breast cancer.

References

13. Stadtmauer EA. Phase III randomized trial of high-dose chemotherapy (HDC) and stem cell support (SCT) shows no difference in overall survival or severe toxicity compared to maintenance chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) for women with metastatic breast cancer who are responding to conventional induction chemotherapy: the Philadelphia Intergroup Study (PB01). *Proc Annu Meet Am Soc Clin Oncol.* 1999;18:1a. Abstract.

**Discussion**

**Dr O'Shaughnessy:** Aside from the patient who is having visceral crisis, do you think there is an established role for combination chemotherapy rather than sequential single-agent therapy?

**Dr Sledge:** Visceral crisis may represent an exception. The other exception might be a patient who has had no prior chemotherapy, is young, has few metastatic sites, and has a good performance status. Based on the M.D. Anderson data, one may ask if this patient should be considered for combination anthracycline-based therapy.

I think the flow of events is what will change this more than anything else. We are in an era where a significant percentage of patients have received prior anthracycline-based adjuvant therapy, and now we’re beginning to see patients who are relapsing after having had prior taxane-based adjuvant therapy. For those patients, single-agent therapy may be the only thing we have available. I see no convincing evidence to suggest that anything is superior to sequential single-agent therapy. Furthermore, many of the combinations are more toxic than single-agent sequential therapy.

**Dr Perez:** Few randomized trials other than E-1193 have compared sequential vs concurrent therapy. The endpoint in many of these phase II combination trials has been response rate. Response rates appear to be higher for combination compared with single-agent therapy, but survival generally is not affected. However, this is not the case with paclitaxel and trastuzumab. In the pivotal trial conducted, median survival was better for concurrent use of these agents instead of sequential use.

**Dr Sledge:** I would suggest that the data we have argue against combination therapy as being superior to single-agent therapy, and not just in E-1193 — in other trials as well. In comparisons of single-agent paclitaxel with CMFP, paclitaxel had superior overall survival as frontline therapy despite having a lower response rate. There may well be a disconnect between response rate and overall survival.

**Dr Muss:** I think that’s true. The classic study was melphalan vs CMF. The CMF had a better response rate, but the median survival was 12 months for both. I think the time to progression is important because it provides more insight concerning the benefit of treatment. Remember that most of a patient’s survival is spent off the drug that’s been used in a study if you have a time to progression of six months and a median survival of 18 months. That means that most of their lifetime is spent receiving something else or nothing.

**Dr Horton:** What would you recommend for patients who have had prior adjuvant anthracycline such as CA or CAF? And what would you do with those who are relapsing after the CA followed by paclitaxel adjuvant therapy?

**Dr Sledge:** I think the question can be answered, in part, by asking when the patient relapsed. Clearly, patients who relapse rapidly after adjuvant therapy are unlikely to benefit from reinstitution of the same therapy. On the other hand, we have a number of studies suggesting that patients who are later relapsers — for instance, with CAF — will still respond to an anthracycline-based regimen. That brings up the issue of whether we can do anything at all for a rapid relaper. My bias is that, for most such patients, we don’t do very well. With all other salvage agents, response rates are fairly low. My strong bias about breast cancer is that, while we’d like to hope that we could find the one drug that would change everything, this is a situation in which we may need to find several cures for several diseases.

Oncologists have been trained over the past two decades to believe that more is better and that more aggressive equals more appropriate. But if you ask what the single most active agent is for the treatment of breast cancer in 1999, the answer is very simple: it’s tamoxifen.

**Dr Sledge** is a consultant for Bristol-Myers Squibb and for Rhône-Poulenc Rorer.

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