Point: Combination Versus Single-Agent Chemotherapy: The Argument for Sequential Single Agents

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Abstract
Metastatic breast cancer is a heterogeneous disease, and treatment decisions depend on several individualized patient and tumor characteristics. Although combination therapy often shows improved response rates in metastatic breast cancer, few studies have shown superiority in overall survival. The choice of combination versus sequential single-agent treatment, therefore, must consider many factors, with no one strategy right for all patients. This article reviews several important clinical trials that address this issue, and argues for single-agent sequential therapy for most patients with metastatic breast cancer. (JNCCN 2007;5:766–770)

Breast cancer is a heterogeneous disease. Most patients diagnosed with early localized disease can expect to be cured. Despite early detection, local treatment, and adjuvant therapy, metastatic relapse will still occur in 40% of patients, and an estimated 41,000 people will die of metastatic breast cancer in the United States in 2007. Treatment decisions in metastatic breast cancer depend on several factors, including specific tumor characteristics such as estrogen, progesterone, and HER2-neu receptor status, and individual patient factors. These factors include the extent of disease and tempo of disease progression, comorbidities, degree of symptomatology, and overall performance status. With more than 20 approved traditional chemotherapy drugs and regimens for metastatic breast cancer, the selection of treatment in the first-line setting and what sequence to use are individualized and tailored to each patient, typically with palliation—not cure—as the treatment goal.

New biologic and targeted agents are beginning to redefine combination therapy, adding another layer of complexity to these decisions. The debate on traditional combination chemotherapy versus sequential single-agent administration continues to be examined in clinical trials. However, no single optimal strategy exists for all patients, and thus the argument could be made that physicians are simply asking the wrong question and are expecting “one size shoe to fit all feet.” The heterogeneity in the biology and behavior of metastatic breast cancer argue for the continued need for flexibility in chemotherapy strategies. Recognizing these factors, this article focuses on traditional chemotherapy choices and presents the case for the use of sequential single-agent chemotherapy over combinations of cytotoxic agents in the treatment of metastatic breast cancer.

Treatment of Metastatic Breast Cancer
Optimal treatment of metastatic breast cancer requires harmony between the art of both science and medicine. No single definitive approach exists for all patients, and deciding what agent to use when depends on many factors. Although polychemotherapy has shown significant improvements in overall survival over monotherapy in the adjuvant setting, the same has not been shown in metastatic breast cancer. Notably, adjuvant systemic therapy for early stage disease is a story with one chapter, whereas the treatment of metastatic breast cancer often involves...
multiple chapters. Over the past 3 decades, this concept has been tested. Although many studies have observed improved response rates, few have shown a survival advantage of combination therapy (Table 1).1–15

The goals of therapy in metastatic breast cancer are typically not curative but rather palliative; thus, the choice of chemotherapy often considers the balance between efficacy and toxicity. Several phase III trials have compared conventional combination chemotherapy regimens with single-agent therapy for metastatic breast cancer. Many of these studies showed improvements in response rates for combination therapy, some in time to progression but none with an advantage in overall survival for combination chemotherapy over single-agent treatment.

A meta-analysis combined several small trials to address the question of single-agent versus combination chemotherapy. Based on 12 small trials of fewer than 150 patients each, Fossati et al.16 concluded that polychemotherapy was superior to single-agent treatment for overall survival (hazard ratio [HR] 0.82; 95% confidence interval [CI], 0.75–0.90). However, this analysis was conducted on clinical trials performed in the pre-taxane era and so did not include any studies using these agents. Two subsequent phase III studies showed improved overall survival for single-agent taxanes over combination chemotherapy.16 One randomized phase III trial involving patients with metastatic breast cancer who had already received an anthracycline compared docetaxel (100 mg/m²) every 3 weeks to mitomycin (12 mg/m²) every 6 weeks plus vinblastine (MV; 6 mg/m²) every 3 weeks. In this study, single-agent docetaxel yielded superior response rates (30.0% vs. 11.6%; P < .0001), time to progression (19 vs. 11 weeks; P = .001), and overall survival (11.4 vs. 8.7 months; P = .0097) compared with combination MV.1

### Table 1 Single-Agent Versus Combination Chemotherapy for Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>N</th>
<th>Response Rate</th>
<th>Time To Progression</th>
<th>Overall Survival Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel vs. mitomycin + vinblastine</td>
<td>392</td>
<td>30% vs. 11.6%</td>
<td>19 vs. 11 wk</td>
<td>11.4 vs. 8.7 mo</td>
</tr>
<tr>
<td>Paclitaxel vs. cyclophosphamide, methotrexate, fluorouracil, prednisone</td>
<td>209</td>
<td>29% vs. 35%</td>
<td>5.3 vs. 6.4 mo</td>
<td>17.3 vs. 13.9 mo</td>
</tr>
<tr>
<td>ECOG 1193: doxorubicin alone vs. paclitaxel alone vs. doxorubicin plus paclitaxel</td>
<td>739</td>
<td>36% vs. 34% vs. 47%</td>
<td>6.0 vs. 6.3 vs. 8.2 mo (TTF)</td>
<td>19.1 vs. 22.5 vs. 22.4 mo</td>
</tr>
<tr>
<td>Epirubicin followed by mitomycin vs. FEC followed by mitomycin + vinblastine</td>
<td>303</td>
<td>48% vs. 55%</td>
<td>8.0 vs. 10.0 mo</td>
<td>16.0 vs. 18.0 mo</td>
</tr>
<tr>
<td>Mitoxantrone vs. fluorouracil, epirubicin, cyclophosphamide</td>
<td>260</td>
<td>57.1% vs. 66.4%</td>
<td>4.4 vs. 6.15 mo</td>
<td>14.1 vs. 15.8 mo</td>
</tr>
<tr>
<td>Doxorubicin vs. doxorubicin + vinorelbin</td>
<td>303</td>
<td>30% vs. 38%</td>
<td>6.1 vs. 6.2 mo</td>
<td>14.4 vs. 13.8 mo</td>
</tr>
<tr>
<td>Epirubicin + vinorelbin vs. epirubicin</td>
<td>387</td>
<td>42% vs. 50%</td>
<td>Not reported</td>
<td>18.0 vs. 19.1 mo</td>
</tr>
<tr>
<td>Epirubicin + epirubicin + cisplatin vs. epirubicin + lonidamine</td>
<td>371</td>
<td>54% vs. 56.4% vs. 60.5%</td>
<td>Reported for arms combined not individually</td>
<td>29.5 vs. 28.8 vs. 29.8 mo</td>
</tr>
<tr>
<td>Docetaxel vs. capecitabine + docetaxel</td>
<td>511</td>
<td>30% vs. 42%</td>
<td>4.1 vs. 6.2 mo</td>
<td>11.5 vs. 14.5 mo</td>
</tr>
<tr>
<td>Paclitaxel vs. gemcitabine + paclitaxel</td>
<td>529</td>
<td>25.6% vs. 39.3%</td>
<td>3.5 vs. 5.4 mo</td>
<td>15.8 vs. 18.5 mo</td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; C, cisplatin; E, epirubicin; ECOG, Eastern Cooperative Oncology Group; FEC, fluorouracil, epirubicin, and cyclophosphamide; L, lonidamine; NS, not significant; T, paclitaxel; TTF, time to tumor progression.
The difference in response rates persisted even in patients with visceral (30.1% vs. 10.9%; \( P < .01 \)) or liver involvement (33.3% vs. 6.8%; \( P < .01 \)). A second phase III study randomized 209 women to receive either paclitaxel (200 mg/m\(^2\)) every 3 weeks or oral cyclophosphamide (100 mg/m\(^2\)/d orally on days 1–14), intravenous methotrexate (40 mg/m\(^2\)) on days 1 and 8, intravenous fluorouracil (FU; 600 mg/m\(^2\)) on days 1 and 8, and prednisone (40 mg/m\(^2\)/d) on days 1 to 14 every 4 weeks (CMFP) in the first-line setting.\(^4\) In that trial, the response rate (29% vs. 35%; \( P = .37 \)) and median progression-free survival (5.3 vs. 6.4 months; \( P = .25 \)) were not statistically different in the paclitaxel and CMFP arms, respectively. After adjustment for known prognostic factors that differed between groups, an improvement in overall survival was seen in the single-agent taxane arm, with a median overall survival of 17.3 months in the paclitaxel arm compared with 13.9 months (\( P = .025 \)) in the patients treated with CMFP.

Few trials have compared combination therapy with the same agents given alone and sequentially. The Eastern Cooperative Oncology Group (ECOG) 1193 trial compared the combination of doxorubicin and paclitaxel against each agent alone, with crossover to the alternative single-agent after progression.\(^7\) This phase III randomized trial of 739 women with metastatic breast cancer compared doxorubicin (60 mg/m\(^2\)) alone with paclitaxel (175 mg/m\(^2\)) with the combination doxorubicin/paclitaxel (doxorubicin, 50 mg/m\(^2\); paclitaxel, 150 mg/m\(^2\)) every 3 weeks. As seen in other studies, the combination arm resulted in a higher response rate (47% doxorubicin/paclitaxel vs. 36% doxorubicin vs. 34% paclitaxel) and slightly longer time to treatment failure (8.0 doxorubicin/paclitaxel vs. 5.8 doxorubicin or 6.0 months paclitaxel) than the single agents used sequentially. However, no difference was observed in overall survival between the arms (22.0 doxorubicin/paclitaxel vs. 18.9 doxorubicin vs. 22.2 months paclitaxel) and quality of life (QoL) measures were similar also. Thus, even the most active agents in metastatic breast cancer (taxanes and anthracyclines used in combination) could not produce superior survival results for patients with metastatic breast cancer over each agent given sequentially.

Another phase III study examined sequential monotherapy versus sequential combination treatment and found no difference in survival outcomes.\(^6\) This trial randomized 303 patients with metastatic breast cancer patients into 2 arms. In one arm, patients received weekly epirubicin (20 mg/m\(^2\)) until progression (or cumulative dose 1000 mg/m\(^2\)) followed by mitomycin C (8 mg/m\(^2\)) every 28 days. The patients in the combination arm received cyclophosphamide (300 mg/m\(^2\)), epirubicin (60 mg/m\(^2\)), and 5-FU (300 mg/m\(^2\)) every 21 days until progression followed by mitomycin C (8 mg/m\(^2\)) plus vinblastine (6 mg/m\(^2\)) every 28 days. No difference was seen in survival, with median overall survival of 16 months in the single-agent arm and 18 months in the combination arm (\( P = .93 \)). This again reinforced the notion of sequential monotherapy as an acceptable option.

After the taxanes were introduced and accepted as a highly effective class of chemotherapy in metastatic breast cancer, 2 phase III studies were conducted comparing a single-agent taxane with a combination including a taxane. These 2 trials have shown a small advantage in overall survival for the combination chemotherapy arm.\(^13,14\) One phase III trial of 511 patients with progressive metastatic breast cancer despite anthracycline treatment examined docetaxel (75 mg/m\(^2\)) with capcitabine (days 1–14 at 1250 mg/m\(^2\) orally twice daily) versus docetaxel (75 mg/m\(^2\)) alone.\(^13\) The combination of docetaxel and capecitabine caused a significant improvement in time to progression (6.2 vs. 4.1 months; \( P = .0001 \)) and overall survival (14.5 vs. 11.5 months; \( P = .0126 \)). However, this combination also caused more grade 3 toxicity (71% vs. 49%), including gastrointestinal side effects, asthenia, and hand–foot syndrome.

A second phase III trial examined paclitaxel (175 mg/m\(^2\)) with or without gemcitabine (1250 mg/m\(^2\) on days 1 and 8) every 21 days in 529 patients as first-line treatment for metastatic breast cancer.\(^14\) Response rate, time-to-progression (5.4 vs. 3.5 months; \( P \leq .0001 \)), and overall survival (18.5 vs. 15.8 months; \( P = .018 \)) were all superior in combination when compared with paclitaxel alone. However, unlike ECOG1193, these trials did not incorporate a crossover approach to the alternative single agent after combination therapy and, therefore, whether overall survival might be equivalent if truly sequential therapy was given is unclear. In the paclitaxel/gemcitabine trial, 14.1% of patients in the paclitaxel monotherapy arm received gemcitabine as a subsequent treatment. In the docetaxel/capecitabine trial, only 27% of patients in the docetaxel arm subsequently received capecitabine, and an unplanned analysis seems to show that these
patients may have had improved survival (HR, 0.500; \(P = .0046\); median survival, 21.0 vs. 12.3 months, respectively) ... This again supports the notion that combination chemotherapy and single-agent sequential therapy yield the same overall outcome.

Ultimately, treatment for metastatic breast cancer will become palliative. Combination chemotherapy is limited by overlapping toxicities that require suboptimal individual drug dosing to allow timely combined delivery. One potential advantage of sequential single-agent treatment is the ability to alternate toxicities such as alopecia, neuropathy, and gastrointestinal and skin toxicities. Although combination chemotherapy may yield improved response rates and equivalent survival compared with sequential single agents, it may be more relevant to consider factors such as QoL. Some would argue that improved response rates and time to tumor progression may act as a surrogate for QoL. However, ECOG 1193 prospectively evaluated patients for QoL and found that they had equivalent scores despite their treatment arm.\(^7\) Some measures of QoL were superior in the sequential monotherapy arm of epirubicin/mitomycin compared with the cyclophosphamide/epirubicin/5-FU/mitomycin/vinblastine trial described above.\(^8\) In this trial, overall days of incapacitation were significantly better in the monotherapy arms at 3, 6, and 9 months (\(P < .001; \ P = .001; \ P = .003\), respectively). In a separate trial of single-agent mitoxantrone (12 mg/m\(^2\)) versus FU (500 mg/m\(^2\)), epirubicin (50 mg/m\(^2\)), and cyclophosphamide (500 mg/m\(^2\)) every 3 weeks, no significant differences were detected in response (57% vs. 66%; \(P = .182\)), time to progression (median 6.2 vs. 4.4 months; \(P = .18\)), or overall survival (14.1 vs. 15.8 months; \(P = .66\)).\(^9\) The only notable difference between the 2 groups was a significant difference in toxicity favoring the monotherapy arm, measured in QoL analysis (\(P = .0001\)). The single-agent mitoxantrone arm also had an overall superior adjusted QoL efficacy score of 3.92 compared with -2.07 for the combination arm. Single-agent sequential therapy may be a more appropriate choice for patients, considering that overall survival is equivalent and toxicities and QoL may be superior.

Conclusions

No universal chemotherapeutic approach to metastatic breast cancer exists. The decision to use combination chemotherapy versus sequential single-agent chemotherapy should be driven by several factors, including the nature and timing of prior therapy, extent of disease burden, tempo of disease, degree of symptomology, and goals of therapy. Cytotoxic combinations are often used in the setting of rapidly progressive visceral, often symptomatic metastatic breast cancer, whereas single-agent chemotherapy is commonly used for most other cases. Sequential single-agent chemotherapy allows for maximal drug dosing and reduces the risk for overlapping toxicities that often limit combinations. With few demonstrated differences in survival, sequential single-agent therapy may allow for the fewest toxicities and superior QoL. Clearly, the emergence of newer targeted agents that lack relative overlapping toxicities with conventional cytotoxic agents (e.g., trastuzumab and bevacizumab) will change the decision process; from all available data in this regard, this is a most welcome refocusing.

References


