Counterpoint: The Argument for Combination Chemotherapy in the Treatment of Metastatic Breast Cancer

Mary Cianfrocca, DO, and William J. Gradishar, MD, *Chicago, Illinois*

Key Words

Metastatic breast cancer, single agent, combination therapy, chemotherapy, polychemotherapy

Abstract

The question of combination versus single-agent chemotherapy in the setting of metastatic breast cancer (MBC) is an often-debated issue. Many single agents have activity in this setting and the potential for significant synergism between chemotherapy agents has led to many combination chemotherapy trials. This article defends the position that combination chemotherapy is the optimal approach for patients with MBC. (*JNCCN* 2007;5:771–773)

The question of combination versus single-agent chemotherapy in the setting of metastatic breast cancer (MBC) is an often-debated issue. Many single agents have activity in this setting and the potential for significant synergism between chemotherapy agents has led to many combination chemotherapy trials. This article defends the position that combination chemotherapy is the optimal approach for patients with MBC.

In the pre-taxane era, early support for combination chemotherapy was provided by the meta-analytic approach. Fossati et al.[1] reviewed 15 randomized clinical trials (2442 patients) comparing polychemotherapy regimens (PCHT) to single agents. Most patients were heavily pretreated. The reported objective response rate favored combination therapy over single-agent therapy (48% vs. 34%, respectively). Survival data were available for 12 of the trials (15 comparisons, 1986 patients). The combined hazard rate favored PCHT regimens (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.75–0.90). This 18% lower risk for death translated into an absolute benefit from PCHT of 9% at 1 year, 5% at 2 years, and 3% at 3 years. Notably, only 2 of 12 trials are associated with an HR for death that clearly favors combination over single-agent therapy. Those 2 trials compare combination regimens to either single-agent cyclophosphamide or 5-fluoruracil. The 10 trials that have doxorubicin or epirubicin as the single-agent comparator do not convincingly show an advantage for combination therapy. Toxicity data from this analysis suggest that combination therapy is better tolerated with significantly less mucositis; however, neurotoxicity was greater compared with single-agent therapy, largely because vincristine was included in combination regimens. Similar results were obtained by the Cochrane Breast Cancer Group, which extracted data from 37 published trials comparing combination versus single-agent chemotherapy.[2] These data, based on 4220 deaths in 5707 women, showed an HR of 0.88 (95% CI, 0.83–0.94; $P < .0001$).

Two large individual, randomized, phase III trials comparing modern-day combinations with single-agent chemotherapy showed a survival benefit for the combination approach. O'Shaughnessy et al.[3] randomized 511 patients with MBC who were pretreated with anthracycline to 21-day cycles of docetaxel 100 mg/m^2 on day 1 compared with docetaxel 75 mg/m^2 on day 1 in combination with capecitabine 1250 mg/m^2 twice daily on days 1 through 14. The capecitabine/docetaxel combination was significantly better than single-agent docetaxel in objective response rate (odds ratio [OR]; 42% vs. 30%;

From Northwestern University, Feinberg School of Medicine, Chicago, Illinois.

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Correspondence: William J. Gradishar, MD, Northwestern University, Feinberg School of Medicine, 676 North St. Clair, Suite 850, Chicago, IL 60611. E-mail: w-gradishar@northwestern.edu

P = .006), time to tumor progression (TTP; 6.1 vs. 4.2 months; HR, 0.652; 95% CI, 0.545–0.780), and overall survival (OS; 14.5 vs. 11.5 months; HR, 0.775; 95% CI, 0.634–0.947). A similar trial using paclitaxel randomized 529 anthracycline-pretreated patients with MBC to 21-day cycles of paclitaxel 175 mg/m^2 on day 1 compared with paclitaxel 175 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on days 1 and 8.[4,5] The gemcitabine/paclitaxel combination was significantly better than single-agent paclitaxel in OR (39.3% vs. 25.6%; P = .0007), TTP (5.4 vs. 3.5 months; P = .0013), and OS (18.5 vs. 15.8 months; P = .18). One-year survival was 70.7% for the combination arm and 60.9% for the single-agent arm.

Both trials have been criticized because of the lack of a planned, controlled crossover at progression on single-agent therapy. But is it possible to show a survival benefit in this disease with a combination versus sequential single-agent study design? The authors argue that it is not. Miles et al.[6] examined the post-study course of patients enrolled in the capecitabine/docetaxel trial. Although the data for patients who received capecitabine after experiencing progression on single-agent docetaxel suggested that sequential and combination therapy might be equivalent, 35% of patients did not receive additional cytotoxic chemotherapy after progression on docetaxel monotherapy. This issue was also suggested in the results of the Eastern Cooperation Oncology Group trial 1193, comparing sequential doxorubicin followed by paclitaxel compared with upfront combination.[7] Although this trial is often used as an argument against combination therapy because no survival benefits were observed for the combination arm, of the 245 patients randomized to doxorubicin and 242 to paclitaxel, only half crossed over to the other single agent (129 and 128, respectively). Furthermore, although one could postulate numerous reasons that an individual patient might not cross over, whether the patients who did cross over may have been "better" patients in terms of disease burden, performance status, and other prognostic factors is reasonable to question. If this is true, showing a significant survival difference between sequential and combination therapy would be very difficult, if not impossible.

These data are also a sobering reminder that physicians may get only one chance at therapy in one third of patients with MBC, as supported by data from Smalley et al.[8] This Southeastern Cancer Study Group trial randomized patients with MBC to a 5-drug combination regimen compared with the same drugs given sequentially. Their analysis suggested that the type of therapy received influenced survival for only half of the patients. Approximately 25% of the patients on each arm died within 4 months of starting treatment and another 25% experienced prolonged survival regardless of therapy. These observations emphasize the heterogeneity of MBC, likely reflecting differences in individual tumor biology. More recent efforts to stratify patients with MBC into distinct groups have been proposed. One example is a prognostic index developed by Yamamoto et al.[9] that separates patients with MBC into low-risk (median survival, 45 months), intermediate risk (median survival, 24 months) and high-risk (median survival, 12 months) categories, taking into account disease-free interval, prior adjuvant chemotherapy, presence of liver metastases, lactate dehydrogenase, and presence of distant metastases. Although the future will hopefully bring improved prognostic and predictive tools, the authors argue that physicians are currently somewhat poor in separating patients who are likely to benefit from a combination approach from those who would do just as well with a sequential single-agent approach. Furthermore, although a combination approach may lead to increased side effects, they are generally manageable and balanced by the potential benefit. Therefore, a combination regimen may be the optimal approach for patients with MBC.

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