Single-Agent or Combination Chemotherapy in Metastatic Breast Cancer

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It is fair to say that combination chemotherapy is the standard of care in metastatic breast cancer. In many ways, however, the burden of proof that it is the standard of care remains with those who advocate combination therapy. Some of the push to consider combination therapy as the standard is provided by a meta-analysis of trials comparing single-agent and combination therapy in this setting, which was reported by Fossati et al in 1998.[1] Although the vast majority of individual trials included in the analysis did not show significant differences in hazard ratios for death, the meta-analysis showed a significant mortality advantage for combination therapy. Yet the total population considered in this meta-analysis (990 patients in combination groups, 996 in single-agent groups) is not large compared with some recent phase III trials in metastatic breast cancer, including one reported by Sledge et al that showed that sequential doxorubicin and paclitaxel was equivalent to the concurrent combination.[2] Further, no studies including taxanes are included in the meta-analysis, raising questions about the application of its findings to contemporary oncology. In addition, the trials included did not examine sequential single-agent treatment, an approach that clearly has merit and that requires additional consideration and study. In addition to the trial reported by Sledge and colleagues, other trials reported since publication of the meta-analysis have failed to show consistent superiority of concurrent combination therapy, including trials showing superiority of paclitaxel over cyclophosphamide (Cytoxan, Neosar)/methotrexate/fluorouracil/prednisone,[3] and docetaxel (Taxotere) over mitomycin (Mutamycin) plus vinblastine.[4] Sequential fluorouracil, epirubicin (Ellence), cyclophosphamide (FEC) followed by mitomycin/vinblastine was as efficacious as epirubicin followed by mitomycin,[5] as was doxorubicin monotherapy compared with doxorubicin/vinorelbine,[6] and mitoxantrone (Novantrone) monotherapy as compared with FEC[7]; toxicities were generally more significant with combination regimens. Ongoing trials with newer concurrent combinations may well provide persuasive evidence of the superiority of this approach. Still, it behooves us as physicians to remember that survival data from a given clinical trial do not provide the whole story of a patient's treatment during the course of her (or his) experience with metastatic breast cancer. In discussing chemotherapeutic approaches in this setting, we are not yet talking about curative regimens, but rather regimens that can prolong survival or time to disease progression and that offer some measure of palliation. Part of the aim of such treatment is to preserve quality of life. In selecting such treatment, it is thus of importance to consider and balance benefit and risk in the form of efficacy and toxicity. Single-agent chemotherapy may pose some advan
regard to reducing negative effects on quality of life by minimizing toxicity. The other papers in this supplement focus on promising combination chemotherapy regimens in metastatic breast cancer. In the absence of definitive evidence of the superiority of this approach—eg, vs sequential single-agent treatment—it is also important to consider the potential merits of single-agent treatment. The most widely used agents in patients with metastatic breast cancer who have already received anthracycline/taxane treatment are gemcitabine (Gemzar), capecitabine (Xeloda), and vinorelbine (Navelbine). There are no data from phase III trials that directly compare these agents to one another. Phase II trials of vinorelbine in refractory disease indicate objective response rates of 16% to 34%.[8,9] In a recent phase III trial in 301 patients with taxane-refractory metastatic breast cancer, liposomal doxorubicin was compared with vinorelbine or mitomycin/vinblastine, based on patient/physician choice; 85% of patients randomized to the comparator group chose vinorelbine treatment rather than the combination. Among 209 evaluable patients, responses included complete response in 3% of the liposomal doxorubicin group vs 3% of the entire comparator group, partial response in 10% vs 12%, and stable disease in 44% vs 37%. Representative toxicities of vinorelbine observed in a phase II study of first-line use are shown in Table 1.[10] One particular concern regarding administration of vinorelbine after a taxane is neurologic toxicity from sequential use of antimicrotubular agents. For example, Fazeny et al reported that of 14 advanced breast cancer patients previously treated with a taxane, 4 had vinorelbine treatment discontinued due to peripheral neuropathy, and 10 had grade 2 constipation.[11] In previously reported phase II studies in taxane-pretreated patients, capecita-


Combination chemotherapy has been associated with response rates of 15% to 25%, response durations of 7.9 to 8.3 months, times to progression of 3.0 to 3.2 months, and overall survival of 12.2 to 12.6 months.[12-14] The most frequent adverse events in this setting are hand-foot syndrome, diarrhea, emesis, and fatigue (Figure 1).[13] In a large phase II trial in 136 patients with taxane- and anthracycline-refractory disease, capecitabine treatment produced a 15% objective response rate, with rates of any/grade 3 or 4 toxicities being 55%/13% for hand-foot syndrome, 60%/7% for nausea/vomiting, and 28%/8% for diarrhea.[14] Similar to vinorelbine and gemcitabine, capecitabine treatment is associated with little to no alopecia. Gemcitabine has been assessed as a single-agent in 11 phase II trials involving more than 300 metastatic breast cancer patients, most of whom had previously received anthracycline or taxane treatment. Objective response rates in these trials ranged from 13% to 42%, based primarily on the extent of previous chemotherapy, and overall median survivals ranged from 11.5 to 17.8 months.[9] In three trials in patients with both anthracycline- and taxane-refractory disease, objective response rates ranged from 18% to 25%.[9,15,16] Grade 3 or 4 toxicities generally consist of neutropenia, with some thrombocytopenia and nausea/vomiting; grade 4 toxicities are infrequent. Table 2 shows toxicities observed in a recent phase II trial of firstline gemcitabine therapy in patients with metastatic breast cancer.[17] Support for the use of combination chemotherapy in metastatic disease was generated by results of a phase III trial reported in 2002, which demonstrated superiority of docetaxel/capecitabine over docetaxel alone in anthracycline-pretreated patients.[18] Furthermore, interim results of a phase III trial comparing gemcitabine/paclitaxel with paclitaxel alone in anthracycline-pretreated disease showed superiority of the gemcitabine/paclitaxel combination.[19] While these studies may encourage the use of combinations rather than single-agent chemotherapies as a first step, they do not inform us regarding the validity and utility of sequential single-agent treatment approaches. Therefore, whether combination treatment is optimal in this setting is still uncertain, and the question of which treatment(s) to use beyond this first step remains to be answered. Another ongoing phase III trial in patients with metastatic disease will provide some answers to the latter issue. In this trial, patients are being randomly assigned to receive docetaxel/gemcitabine followed by capecitabine or docetaxel/capecitabine followed by gem-

**Figure 1: Adverse Events**—Most frequent adverse events with capecitabine single-agent treatment in metastatic breast cancer. HFS = hand-foot syndrome.[12-14]
Results of this trial promise to be helpful in planning treatment beyond the first chapter in the course of metastatic disease. The other contributions to this supplement review the rationale for use of and the outcomes observed with the promising combination of gemcitabine and paclitaxel. Joyce O'Shaughnessy reviews compelling data supporting use of the gemcitabine/paclitaxel combination and describes interim analysis findings of a multinational phase III trial comparing gemcitabine/paclitaxel with paclitaxel alone in patients with metastatic breast cancer. Carlos Delfino and colleagues explore phase II trial results for gemcitabine/paclitaxel as first-line treatment of advanced breast cancer. Andr Murad updates findings of a phase II trial of gemcitabine/paclitaxel as salvage therapy for metastatic disease. George Sledge discusses the rationale for the triple combination of gemcitabine/paclitaxel plus trastuzumab (Herceptin) and reviews findings of a phase II trial of the combination in patients with HER2-positive disease. Christoph Zielinski discusses the rationale for gemcitabine/paclitaxel/anthracycline combinations and reviews available information from trials examining gemcitabine/paclitaxel in combination with doxorubicin or epirubicin.
The data reviewed herein demonstrate that gemcitabine combinations are highly active and well tolerated in the setting of metastatic disease, indicating an important role for this agent in breast cancer. Optimizing use of such promising agents and combinations throughout the many chapters of a patient's experience with breast cancer is a central challenge in patient care. Recognition of the heterogeneity in the biology and behavior of metastatic breast cancer will most certainly imply heterogeneity in treatment strategies; this is indeed where the art and science of medical oncology merge.

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