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EDITORIAL

Are Anthracycline-Taxane Regimens the New Standard of Care in the Treatment of Metastatic Breast Cancer?

METASTATIC BREAST cancer (MBC) is a major public health problem for women in the United States and is the second most common cause of cancer-related death for American women. In 2001, nearly 40,000 people died from this disease.[1] The management of MBC is a major clinical challenge for medical oncologists. Despite all available hormonal and chemotherapy agents, MBC is largely incurable,[2,3] and few (< 10%) patients remain disease free beyond 5 years.[4,5] Therefore, our current therapeutic goals are palliative, including symptom control, quality-of-life improvement, disease control, and prolongation of survival. Survival and response to therapy are affected by several factors, including performance status, disease-free interval, tumor characteristics (presence of hormonal or epidermal growth factor receptors), previous therapy, site of metastasis, and extent of disease.

After 20 years of a relative drought in drug development, we have witnessed the approval of 10 new agents for the treatment of MBC in the last 8 years.[6-22] Several of these agents changed the natural history of advanced breast cancer and replaced older agents that we had used for decades. The role of chemotherapy for the palliative treatment of patients with hormone-insensitive (estrogen receptor/progesterone receptor [ER/PR]-negative) or hormonal therapy-refractory MBC is well established.[2,3,23-24] The most important cytotoxic agents employed between the 1970s and the mid-1990s were the anthracyclines (doxorubicin and epirubicin). Anthracycline-containing regimens were proven superior to regimens that did not include anthracyclines in randomized clinical trials.[23,24] Therefore, for two decades, anthracycline therapy was the backbone of palliative regimens for patients with MBC. However, within the past decade, three new cytotoxic agents (paclitaxel, docetaxel, and capecitabine) were approved for the treatment of MBC. All three agents improved the overall survival (OS) of patients with MBC in well-designed controlled clinical trials.[15,17,20]

The taxanes, paclitaxel and docetaxel, are microtubule inhibitors that bind reversibly to the beta subunit of tubulin, inducing microtubule polymerization and inhibiting microtubule depolymerization, leading to cell arrest at the G_2/M phase of the cell cycle.[25-27] The taxanes also induce apoptosis in breast cancer cells and inhibit tumor angiogenesis. Single-agent paclitaxel produced equivalent survival when compared with a commonly used combination, such as cyclophosphamide, methotrexate, fluorouracil, and prednisone.[14] Response rates in these comparisons were usually similar, as well. Comparisons of single-agent docetaxel to doxorubicin or combinations such as mitomycin/vinblastine or methotrexate/fluorouracil favored the taxane.[17,18] The integration of this class of agents either alone[17] or in combination[15,20] with other active agents into the management of MBC resulted in improved OS of both untreated[15] and refractory MBC compared with regimens lacking a taxane.[17,20]

Several different doses and schedules of paclitaxel and docetaxel have been investigated, and the optimal method of administration has yet to be determined. The taxanes have been combined with a variety of chemotherapeutic agents with different mechanisms of action. However, few have a solid, biologically driven preclinical rationale. The most commonly tested of these combinations includes a taxane and an anthracycline. There is no documented synergy in preclinical experiments, but as the two most active groups of cytotoxic agents, their empirical combination was a natural step. Early trials incorporated prolonged infusions of both paclitaxel (24 to 72 hours) and doxorubicin (48 to 72 hours) and were associated with pharmacokinetic interactions that resulted in severe neutropenia and gastrointestinal toxicity,[28] secondary to delayed hepatic clearance of doxorubicin. Sequencing paclitaxel after doxorubicin and reducing the duration of infusion of both drugs reduced toxicity without altering the efficacy; however, significant pharmacokinetic interaction remained.[29] The bolus and short-infusion doxorubicin/paclitaxel regimens were associated with a high incidence of cardiotoxicity. Strategies to reduce cardiac toxicity associated with these combinations included substituting epirubicin or liposomal doxorubicin for doxorubicin, limiting the doxorubicin per cycle to 50 mg/m^2 and the cumulative doxorubicin dose to 360 mg/m^2, and separating the agents by an interval longer than 4 hours to avoid pharmacokinetic interactions.

The combinations of docetaxel with anthracyclines are also highly active regimens for MBC. The dose-limiting toxicity

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observed in these regimens was myelosuppression.[30] However, doxorubicin/docetaxel or epirubicin/docetaxel combinations did not significantly increase the risk of cardiotoxicity.

Six phase III randomized phase trials have compared anthracycline-taxane combinations to standard anthracycline-based combinations.[15,31-35] Three have been peer-reviewed and published.[15,31,32] The Eastern European phase III randomized trial compared the doxorubicin (50 mg/m^2 day 1) and paclitaxel (220 mg/m^2 day 2) combination (AT) with fluorouracil (500 mg/m^2 intravenously [IV] on day 1), doxorubicin (50 mg/m^2 IV on day 1), and cyclophosphamide (500 mg/m^2 day 1) combined (FAC) as first-line therapy for patients with MBC. In this study, response rates (68% *v* 46%), time to progression (TTP; 8.3 *v* 6.2 months), and OS (22.7 *v* 18.3 months) were significantly better in the AT arm. The incidence of cardiotoxicity was similarly low in both arms.

Nabholtz et al describe the second trial in this issue of the Journal.[31] This was a well-designed, multicenter, multinational randomized phase III trial that enrolled 429 patients. This trial randomly assigned patients to an AT combination (doxorubicin [Adriamycin] 50 mg/m^2 and docetaxel 75 mg/m^2 day 1) or a combination of doxorubicin and cyclophosphamide (AC; 60 mg/m^2, 600 mg/m^{2}day 1, respectively) as first-line therapy for patients with anthracycline-naive MBC. In this study, response rates (59% *v* 47%) and TTP (37.3 *v* 31.9 weeks) were significantly better in the AT arm. However, OS durations (22.5 *v* 21.7 months) and quality-of-life measurements were similar in the two arms of the trial. The incidence of cardiotoxicity was similar in both arms, but the rate of neutropenic fever was significantly higher in the AT arm, although there were no toxic deaths. Grade 3 diarrhea and moderate asthenia were more common in the AT arm (8% *v* 1%). None of the other four randomized trials demonstrated improvement in OS. The results of the European Organization for Research and Treatment of Cancer phase III randomized study were just published in the Journal.[32] Patients were randomly assigned to doxorubicin and cyclophosphamide (AC) or doxorubicin and paclitaxel (AT). The objective response rate and TTP were not significantly different, nor was there a difference in median OS (20.5 *v* 20.6 months). Neutropenic fever was also significantly lower in the AC arm (9% *v* 32%).

The phase III randomized trial comparing TAC with FAC[33] demonstrated a significantly higher response rate in the TAC arm (54% *v* 43%). However, TAC failed to improve TTP or OS compared with FAC (21 *v* 22 months). A German randomized trial compared epirubicin/paclitaxel (ET) with epirubicin/cyclophosphamide. No significant differences in outcome were reported.[34] The largest of the six of randomized trials was conducted in the United Kingdom and enrolled 705 patients. The objective response rate was higher in the ET arm (67% *v* 56%). However, this trial again demonstrated equivalence in TTP and OS.[35] Severe mucositis and neurotoxicity were of higher incidence in the ET arm.

In summary, six phase III trials comparing anthracycline/taxane combinations with anthracycline combinations without taxanes have been conducted. Response rates favored the taxane arm in four trials, and none favored the arm without a taxane. No significant improvements in complete remission have been reported. TTP favored the taxane arm in two of six studies, and in one study there was a significant survival advantage for the taxane-containing treatment group. There was no direct comparison between two-drug (AT/ET) and three-drug (TAC/TEC) anthracycline/taxane-containing combinations.

With this information at hand, how do we apply these results to clinical practice, and how do we formulate the next generation of relevant questions? Improvements in response rates and TTP are encouraging but are not compelling enough in the absence of a consistent survival benefit to prefer the taxane/anthracycline regimens over older, more established regimens. There might be patients for whom obtaining a higher response rate would be an indication to prefer these regimens. These patients would include those with symptomatic metastatic disease, those with rapidly advancing visceral disease, and those for whom experiencing a response is of subjective importance. However, for the majority of patients, other approaches, including established combinations or sequential single-agent therapy, would be equally acceptable.

Can we use anthracyclines and taxanes more effectively? When combining myelosuppressive drugs, dose reductions are necessary to develop a tolerable regimen. This is certainly true of the anthracycline/taxane combinations. However, there is little evidence of a dose response for anthracyclines above a threshold dose, and such doses are clearly possible within the taxane/anthracycline combinations. There is only a marginal signal for a dose response for paclitaxel, especially in MBC; this information is not well established for docetaxel. However, it is difficult to believe that the differences in dose that fail to affect survival after single-agent taxane therapy would influence survival when given in combination. Although dose-intensity above the minimal dose threshold might not improve outcome, dose-dense strategies are still under active consideration. Preliminary results of a large Intergroup trial would indicate that a dose-dense administration of a taxane and anthracycline-containing adjuvant chemotherapy regimen would yield improved results.[36] Confirmation of these results from other prospective trials would be highly desirable before general adoption into practice.

Would the sequential use of these two classes of agents be more successful? There is incomplete cross-resistance between the anthracyclines and the taxanes. The only trial that addresses the issue of schedule/sequence is the Eastern Cooperative Oncology Group trial.[37] This trial randomly assigned patients to doxorubicin (60 mg/m^2 as a bolus) versus paclitaxel (175 mg/m^2 over 24 hours) versus a combination of the two agents (doxorubicin 50 mg/m^2 and paclitaxel 150 mg/m^2 over 24 hours). The objective response rates were similar for single-agent doxorubicin and paclitaxel (34% *v* 33%, respectively) but higher for the combination arm (46%). The TTP was significantly longer in the combination arm. However, the median OS durations were not significantly different among the three arms (20 *v* 22 *v* 23 months, respectively). Although sequential single-agent therapy might be easier to administer, it produces no improvement in the efficacy of treatment or the patients' quality of life.

Another important consideration is the clinical applicability of these results. Few patients present de novo with MBC, and the great majority of patients who later develop MBC are now

receiving anthracycline-based adjuvant therapy. In fact, paclitaxel is approved by the United States Food and Drug Administration for adjuvant chemotherapy of primary breast cancer, so many patients with lymph node-positive breast cancer also receive a taxane following (or in combination with) anthracycline-based adjuvant chemotherapy. Therefore, fewer patients will be candidates for anthracycline/taxane combinations in the metastatic setting. Those patients who were not exposed to anthracyclines or taxanes in the adjuvant setting, such as those relapsing after adjuvant cyclophosphamide, methotrexate, and fluorouracil, especially if they are symptomatic or are at risk for a visceral crisis, would be candidates for a taxane/anthracycline combination in the metastatic setting. If only a small subset of patients is eligible for these regimens in the first place, then the results of the phase III trials summarized above will best serve to generate hypotheses to be considered in earlier stages of breast cancer in the adjuvant and neoadjuvant setting. There are indeed preliminary data that indicate that the addition of a taxane improves the efficacy of standard anthracycline-containing combinations.[38] Whether sequential or simultaneous combinations with taxanes would be more effective or better tolerated remains to be determined. Similarly, the question of whether two-drug or three-drug combinations will be optimal awaits mature results of well-designed clinical trials.

The development of technological advances, such as genomics and proteomics, might make it possible to select subsets of patients most (and least) likely to benefit from a taxane/anthracycline combination. Such an approach would enhance the efficacy of the regimen in appropriately selected patients while avoiding the toxicity of the regimen for those unlikely to benefit from this treatment.

Taxanes are also under evaluation in non-anthracycline-containing combinations. Prominent among these are the platin/taxane, vinorelbine/taxane, and fluoropyrimidine/taxane combinations. Whether these regimens will have a higher therapeutic index or whether they contribute more to the survival of patients with MBC remains to be established.

Integrating these new hormonal, chemotherapeutic, and biologic agents into our current armamentarium is clearly a major challenge. Some of these agents have changed modestly the natural history of breast cancer. Our patients are getting better and longer palliation of their symptoms and are living longer.[39] Further research is needed to clarify the optimal dose, schedule, sequence, and combinations of these agents. In summary, AT and similar regimens represent new options for selected patients with anthracycline-naive MBC. Symptomatic patients with good performance status; bulky disease; visceral involvement; and for whom adjuvant cyclophosphamide, methotrexate, and fluorouracil treatment has failed should be considered candidates for this combination.

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