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Chemotherapy of Metastatic Breast Cancer: What to Expect in 2001 and Beyond

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Key Words. Breast neoplasm · Chemotherapy · Biologic therapy · Prognostic markers

ABSTRACT

Chemotherapy plays an important role in the management of metastatic breast cancer. The anthracyclines (doxorubicin, epirubicin) and the taxanes (paclitaxel, docetaxel) are considered the most active agents for patients with advanced breast cancer. Traditionally, the anthracyclines have been used in combination with cyclophosphamide and 5-fluorouracil (FAC, FEC). The taxanes have single-agent activity similar to older combination chemotherapy treatments. There is great interest in developing anthracycline/taxane combinations. Capecitabine is indicated for patients who progress after anthracycline and taxane therapy. Vinorelbine and gemcitabine have activity in patients with metastatic breast cancer and are commonly used as third- and fourth-line palliative therapy. The role of high-dose chemotherapy is not well-defined and remains experimental. Novel cytotoxic therapy strategies include the development of anthracycline, taxane, and oral fluoropyrimidine analogues; antifolates; topoisomerase I inhibitors, and multidrug resistance inhibitors.

A better understanding of the biology of breast cancer is providing novel treatment approaches. Oncogenes and tumor-suppressor genes are emerging as important targets for therapy. Trastuzumab, a monoclonal antibody directed against the Her-2/neu protein, has been shown to prolong survival in patients with metastatic breast cancer. Other novel biologic therapies interfere with signal transduction pathways and angiogenesis. The challenge for the next decade will be to integrate these promising agents in the management of metastatic and primary breast cancer. The Oncologist 2001;6:133-146

INTRODUCTION

Breast cancer is the most common malignancy and the second most common cause of cancer-related death in Western European and North American women. In 2001, about 192,200 women will be diagnosed with breast cancer in the United States, and nearly 40,800 will die from the disease [1]. Although the incidence of breast cancer is increasing, the mortality rates from breast cancer have decreased approximately 1.9% per year since 1990 in the United States. This is most likely due to earlier diagnosis through mammographic screening and the increased use of adjuvant systemic therapy [2]. However, when breast cancer cells metastasize to distant organs, the disease is typically incurable by conventional treatments (hormone therapy and chemotherapy).

A variety of cytotoxic and hormonal agents provide significant palliation for patients with metastatic breast cancer. The role of cytotoxic chemotherapy is well established for patients with life-threatening disease that requires rapid tumor control. Chemotherapy is also the treatment of choice for patients with hormone-insensitive breast cancer. The most active cytotoxic agents include alkylating drugs, antimitabolites, vinca alkaloids, anthracyclines, and taxanes. Used as single agents, these various cytotoxics produce major objective responses in 20%-80% of patients with metastatic breast cancer [3-5]. However, complete responses (CR) are rare and less than 20% of patients who achieve a CR maintain that status beyond 5 years [6]. A variety of systemic treatments have been used, either alone or in combination, in an attempt to reinduce remission in
patients for whom initial chemotherapy fails. However, the response rates (RR) in these programs have been considerably lower than those for initial chemotherapy, and the durations of response and survival have been shorter. For these patients the goals of treatment are to maintain a good quality of life and prolong survival. This manuscript reviews the current use of cytotoxic chemotherapy and describes ongoing efforts to develop novel agents for metastatic breast cancer.

**ANTHRACYCLINES**

For decades, the systemic treatment of patients with metastatic breast cancer has been based on hormonal manipulations and the rational use of cytotoxic agents. These include DNA alkylators and intercalators, antimitabolites, antitumor antibiotics, and tubulin inhibitors [7]. The chemotherapy regimens most commonly used in the late 1960s consisted of cyclophosphamide, methotrexate, 5-fluorouracil (5-FU), prednisone, and vincristine combinations (CMF, CMFP, CMFVP). These regimens produced objective RR in 50%-60% of patients, including a 5%-10% CR rate. The duration of response ranged from 6 to 9 months and the overall survival rate was 15-18 months [3].

The 1970s were marked by the clinical development of doxorubicin (Adriamycin®; Pharmacia & Upjohn, Inc.; Portage, MI), and epirubicin (Ellence®; Pharmacia & Upjohn, Inc.). Regimens that included an anthracycline were superior to regimes that did not, at the expense of higher toxicity.

Single-agent doxorubicin produced RR of 35%-50% when given as front-line therapy. In patients previously treated with alkylator-based chemotherapy, RR were 25%-30%. Doxorubicin-containing combinations produced overall responses in the range of 50%-60% [3]. The duration of response was 8-15 months, and the median survival following a doxorubicin-alkylator agent combination was reported in the range of 17-25 months. The most commonly used doxorubicin-based combinations are AC (doxorubicin, cyclophosphamide), and FAC (5-fluorouracil, doxorubicin, cyclophosphamide) [8]. Several randomized clinical trials showed higher RR and improvements in disease-free survival for patients treated with FAC compared to CMF [9-14]. Other studies showed equivalence between these regimens. However, no randomized study has shown superior results with CMF over FAC. Although more efficacious in the metastatic setting, doxorubicin-containing regimens are more toxic than CMF-type regimens. Almost all patients treated with doxorubicin develop alopecia, and some degree of nausea and vomiting; approximately 2%-4% of patients develop congestive heart failure (CHF); and extravasation may cause severe skin and subcutaneous damage. The degree of myelosuppression is similar for CMF and FAC regimens.

Doxil® (Alza Pharmaceuticals; Mountain View, CA) is a pegylated liposomal doxorubicin recently approved for the treatment of patients with ovarian cancer. The dose-limiting toxicity of Doxil is hand-foot syndrome and stomatitis [15]. These side effects are dose- and schedule-dependent [16]. In a multicenter phase II study, Doxil® 45 mg/m² was administered every 4 weeks to patients with metastatic breast cancer. Most patients had been exposed to prior chemotherapy, including anthracyclines. Myelosuppression was mild. The RR was 31% [17]. TLC-D99 (Evacet®; The Liposome Company Inc.; Princeton, NJ) is another liposomal formulation of doxorubicin that is being evaluated for patients with metastatic breast cancer. Phase II clinical trials indicate that this is a safe and active agent for patients with metastatic breast cancer [18, 19].

Epirubicin is a doxorubicin analogue that has been shown to have similar efficacy and somewhat less toxicity than doxorubicin at equipotent therapeutic doses [20]. Both agents bind DNA and inhibit RNA and protein synthesis. They also generate cytotoxic-free radicals, block DNA cleavage by topoisomerase II, inhibit helicase activity, and interfere with DNA replication and transcription. The mean elimination half-life of epirubicin and its circulating metabolite, epirubicinol, are shorter than the half-lives of doxorubicin and doxorubicinol, respectively [21]. It has been suggested that the pharmacokinetic characteristics of doxorubicin and epirubicin are responsible for their different toxicity profiles. A randomized clinical trial compared FAC with FEC at equimolar doses of doxorubicin and epirubicin (50 mg/m²) [22]. In this study, the FEC regimen was as effective as FAC in terms of RR, time to progression, and survival. The FEC regimen was associated with less gastrointestinal, hematologic, and cardiac toxicity. However, the optimal dose of epirubicin is not known. Another randomized trial compared single-agent epirubicin with FEC-75 (epirubicin 75 mg/m²) and FEC-50 (epirubicin 50 mg/m²) [23]. In this study FEC was superior to single-agent epirubicin, and FEC-75 produced higher RR than FEC-50. Survival was better for FEC-75 (p = 0.006). Another area of interest is the optimal duration of chemotherapy for patients with metastatic breast cancer. A large randomized clinical trial evaluated the duration of FEC therapy. Patients were randomized to FEC-75 for 11 cycles; FEC-100 for four cycles followed by eight cycles of FEC-50; or to four cycles of FEC-100. Patients randomized to the latter group were treated with the same regimen (FEC-100) at the time of progression. Although the RR was higher using the FEC-100 regimen, the overall survival rate was similar for the three groups [24]. Epirubicin is also effective as adjuvant therapy for patients with stage II breast cancer and has recently been approved in the U.S. for this indication.
**Taxanes: Drugs of the 1990s**

The introduction of paclitaxel (Taxol®, Bristol-Myers Squibb Company; Princeton, NJ) and docetaxel (Taxotere®, Aventis Pharmaceuticals; Collegeville, PA) in the 1990s followed a 15-year period of little progress in the development of new drugs for breast cancer. Both agents bind reversibly to the beta subunit of tubulin and induce tubulin polymerization [25]. Normal microtubules need to maintain a balance between polymerization and depolymerization. The taxanes disrupt this balance, leading to arrest at the G2/M phase of the cell cycle. In addition, the taxanes inactivate the Bcl-2 protein and induce apoptosis in breast cancer cells in vitro [26, 27].

**Paclitaxel**

Paclitaxel is a natural product isolated from the bark of the Pacific yew tree, *Taxus brevifolia* [28]. In patients with anthracycline-resistant metastatic breast cancer, paclitaxel produced RR of 6% to 48%. As front-line therapy in patients not previously exposed to chemotherapy, the RR were 32% to 62% [29-33]. Several different doses and schedules of paclitaxel have been investigated and the optimal administration regimen has yet to be determined. The recommended doses for single-agent paclitaxel are 135 mg/m² to 175 mg/m² given over 3 hours [34]. Higher doses and longer schedules of administration are safe, but none have been shown to be definitely superior to the “standard” 175 mg/m² given as a 3-hour infusion [33, 35, 36]. A randomized study showed that paclitaxel (200 mg/m² over 3 hours) was as effective as a combination of cyclophosphamide, methotrexate, fluorouracil, and prednisone (CMFP) in untreated metastatic breast cancer patients. Although RR were similar, the quality of life was improved for patients treated with paclitaxel [37]. The median time to progression was longer with CMFP (6.4 months versus 5.5 months), but median survival was higher with paclitaxel (16.5 months versus 11.3 months). Two large randomized trials have compared paclitaxel to doxorubicin as front-line therapy for patients with metastatic breast cancer. A multicenter trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) randomized patients to paclitaxel (200 mg/m² over 3 hours) versus doxorubicin (75 mg/m² bolus) [38]. In this study, which allowed cross-over to the alternate therapy, RR and median progression-free survival were significantly better with doxorubicin (RR = 41%) compared with paclitaxel (RR = 25%). In another large randomized study conducted by the Eastern Cooperative Oncology Group (ECOG), doxorubicin (60 mg/m² as a bolus) was directly compared with paclitaxel (175 mg/m² over 24 hours) and the combination of the two agents (doxorubicin 50 mg/m² and paclitaxel 150 mg/m² over 24 hours) [39]. In this three-arm trial, RR were similar between the doxorubicin (RR = 34%) and the paclitaxel (RR = 33%) arms of the study. Median time to treatment failure and median overall survival were not significantly different between the two single-agent arms of the study. Patients on the single-agent arms of this study were crossed over to the other agent upon progression. This limits the ability to detect differences in overall survival between the groups. However, according to the available data, paclitaxel and doxorubicin appear to have similar antitumor activity. Partial responses (PR) were seen in 20% of patients who crossed over from doxorubicin to paclitaxel and in 14% of patients who crossed over from doxorubicin to paclitaxel (20%), and from paclitaxel to doxorubicin (14%).

**Docetaxel**

Docetaxel is a second-generation taxane, purified from the needles of the European yew tree, *Taxus baccata* [40]. Docetaxel has been recommended for breast cancer at doses ranging from 60-100 mg/m² administered as a 1-hour infusion. A randomized clinical trial is currently exploring the efficacy of three doses of docetaxel: 60 mg/m², 75 mg/m² and 100 mg/m². Docetaxel is a highly effective agent for metastatic breast cancer. In previously untreated patients, RR range from 40%-68%, better than any other single-agent chemotherapy [41, 42]. Docetaxel is particularly active in patients with anthracycline-resistant breast cancer. In two studies published simultaneously, the objective RR to docetaxel in patients with breast cancer resistant to anthracyclines were 53% and 57%, respectively [43, 44]. This excellent RR was confirmed in randomized trials. In one study, docetaxel 100 mg/m² over 1 hour was compared to mitomycin C plus vindesine in patients with anthracycline-resistant metastatic breast cancer. Patients treated with docetaxel had significantly better RR (30% versus 11.6%), time to progression (19 versus 11 weeks), and overall survival (11.4 versus 8.7 months) [45]. Another study compared docetaxel (100 mg/m² over 1 hour) with sequential methotrexate (200 mg/m² day 1) and 5-FU (600 mg/m² days 1, 8) administered to patients with advanced anthracycline-resistant breast cancer [46]. Preliminary results from this phase III trial indicate that docetaxel appears to be more active than the sequential combination of methotrexate and 5-FU. RR (42% versus 19%) and median time to progression (6 months versus 3 months) were significantly better in the docetaxel arm, again demonstrating that docetaxel is effective therapy against anthracycline-resistant breast cancer.

A randomized trial compared docetaxel (100 mg/m² over 1 hour) with doxorubicin (75 mg/m² bolus) in patients with metastatic breast cancer who had failed an alkylating-containing regimen [47]. Docetaxel demonstrated significantly better RR compared to doxorubicin in this patient population.
(47% versus 32%). Of the 326 evaluable patients, 49% were classified with resistant disease, having progressed on prior chemotherapy, 70% of patients received docetaxel or doxorubicin as second-line therapy for metastatic breast cancer, and 30% received this regimen as first-line therapy for metastatic disease after having relapsed >12 months after adjuvant therapy. These results suggest that docetaxel may be a better agent against breast cancer than doxorubicin. Docetaxel also appears to have activity in breast cancer patients that exhibit resistance to paclitaxel [48].

**WEEKLY TAXANES**

The taxanes can be safely administered on weekly schedules with preserved efficacy. However, administration of taxanes on a weekly schedule significantly changes their toxicity profile. Both agents cause mild myelosuppression and less hypersensitivity reactions compared to 3-weekly schedules, even if they are administered without interruption. The dose-limiting toxicity for weekly paclitaxel is peripheral neuropathy. The optimal starting dose is 80 mg/m²/week. Seidman et al. [49] reported an RR of 53% in patients treated with weekly paclitaxel. A multicenter study reported a lower RR of 25% [50]. For weekly docetaxel, the optimal dose is 35-40 mg/m²/week, and the most common limiting toxicities are neutropenia and fatigue [51]. In a phase II study of weekly docetaxel, the RR was 41% (95% confidence interval, 24% to 61%), all occurring within the first two cycles [52].

In summary, both taxanes are excellent choices for the first- and second-line treatment of patients with metastatic breast cancer. In patients with anthracycline-resistant breast cancer, docetaxel activity is impressively and consistently high in all trials reported in the literature. Compared to paclitaxel, docetaxel appears to produce superior results in this subset of patients. However, comparisons are indirect and potentially biased due to the lack of direct comparative data.

**CAPECITABINE**

Capecitabine (Xeloda®; Hoffmann-La Roche Inc.; Nutley, NJ) is the first oral fluoropyrimidine approved by the Food and Drug Administration (FDA) for the treatment of patients with metastatic breast cancer who failed prior doxorubicin and paclitaxel chemotherapy. Capecitabine is a prodrug that is activated at the tumor site by a series of enzymatic reactions. Clinically, its activity mimics continuous infusional 5-FU. Capecitabine is well-absorbed and not altered by the small bowel intestinal mucosa. It then undergoes a three-step conversion process to the active form, 5-FU. The first step of this process occurs in the liver, where it is converted to 5'-deoxy-5-fluorocytidine by carboxylesterase. It is then converted to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase in liver and also tumor tissues. Further metabolism of 5'-DFUR occurs selectively within tumors by thymidine synthetase to 5-FU. This causes less direct 5-FU release into the bowel, and reduces the potential for diarrhea.

The first phase II study of capcitabine in breast cancer involved 162 women previously treated with paclitaxel for metastatic disease [53]. Of these, 37 (23%) were classified as paclitaxel failures, and 124 (77%) as paclitaxel-resistant. Of the 147 patients who had also received previous anthracycline treatment, 42 were designated as having failed therapy, and 67 as being anthracycline-resistant. Capecitabine was administered as 2,510 mg/m²/day in two divided doses for 14 days, followed by 1 week of rest. This cycle was repeated every 3 weeks. Using this regimen, 27 (20%) of the 135 women with measurable disease demonstrated complete (n = 3) or partial (n = 24) responses. All women who responded to therapy were resistant to or had failed paclitaxel, and all had received an anthracycline. The median duration of response for these women was 8.1 months, and median survival time was 12.8 months. Furthermore, of 51 patients with considerable tumor-related pain at baseline, capcitabine treatment reduced the pain intensity on a visual analog scale by more than half in 47%. Two additional phase II studies confirmed this response to treatment in women with previously treated breast cancer [54, 55]. O’Shaughnesssey and colleagues [54] randomized older women (>55 years) to CMF (cyclophosphamide 600 mg/m², methotrexate 40 mg/m², 5-FU 600 mg/m²) or capcitabine as front-line chemotherapy for metastatic breast cancer. The overall RR was 30% for capcitabine and 16% for CMF. Five CR were observed in the capcitabine group. There was no difference in the median time to progression. Similar levels of emesis, stomatitis, and fatigue were observed for both groups, whereas more cases of diarrhea (8%) and hand-foot syndrome (16%) were seen in patients treated with capcitabine. Alopecia and myelosuppression were more common for patients receiving CMF. These studies demonstrated that capcitabine is an active agent in the treatment of metastatic breast cancer, and that significant responses can be achieved in women already treated with anthracyclines and taxanes (Table I). The FDA-approved dose and schedule are 2,510 mg/m²/day given orally in two divided doses for 14 days, followed by 1 week of rest. However, retrospective studies suggest that a slightly lower starting dose (2,000 mg/m²/day) is better tolerated with preserved efficacy [56, 57].

**VINORELBINE**

Vinorelbine (Navelbine®; Glaxo Wellcome Inc.; Research Triangle Park, NC) is a novel vinca alkaloid that has shown significant activity against breast cancer. Vinorelbine...
is a cell cycle-specific microtubule inhibitor. In contrast to the taxanes, vinorelbine destabilizes the microtubules. In vitro studies showed a selective effect on non-neuronal microtubules, which may explain the decreased neurotoxicity of vinorelbine compared with other vinca alkaloids [58]. As a single agent, vinorelbine produced RR of 20%-40% when delivered i.v. at 25-35 mg/m² on days 1 and 8 of a 3-week cycle. Objective RR have been reported in patients who had progressed after anthracyclines and taxanes [59-62]. This agent is particularly well-tolerated in elderly patients [63]. Long infusions and dose-intensive regimens administered with the addition of hematopoietic growth factors to support blood counts are feasible [64, 65]. However, it is not clear that these approaches would be superior to the standard weekly administration of vinorelbine.

The low incidence of alopecia and other nonhematologic toxicities makes vinorelbine particularly attractive as a safe agent for the palliative treatment of metastatic breast cancer. Granulocytopenia, the dose-limiting toxicity of this agent, is transient and, at current recommended dose levels, rarely results in life-threatening consequences. Vinorelbine is a vesicant and should be administered carefully to avoid tissue extravasation. Perhaps one of the main applications of vinorelbine will be in combination with novel biologic agents, as shown with trastuzumab monoclonal antibody (mAb) therapy [66].

**Gemcitabine**

Gemcitabine (Gemzar®; Eli Lilly; Indianapolis, IN) is a nucleotide analogue that inhibits DNA synthesis. Gemcitabine is an effective cytotoxic against a variety of solid tumor cell lines in vitro and in vivo [67]. Carmichael et al. [68] evaluated the safety and efficacy of gemcitabine as a single agent (800 mg/m²/week for 3 weeks of a 4-week cycle). In this metastatic breast cancer study the RR was 25%. The median survival was 11.5 months. The main toxicity was hematologic, although only 1 of 44 patients developed neutropenic sepsis. Other phase II studies suggest that single-agent gemcitabine is safe and effective and should be an option as salvage chemotherapy for patients who failed anthracycline-, taxane-, and fluorocytidine-based therapy.

**Combination versus Sequential Chemotherapy**

The role of single-agent chemotherapy versus combination chemotherapy has been a controversial area for more than 30 years. When evaluating older regimens such as FAC, FEC, or CMF, polychemotherapy regimens produce higher rates than single agents. Anthracycline-containing regimens are superior to non-anthracycline-containing regimens. However, it is not clear that polychemotherapy regimens result in improved survival when compared to the same agents administered sequentially. Chlebowski et al. [69] randomized 222 women with metastatic breast cancer to CMFP ± V versus sequential single-agent therapy. In this study there was no difference in overall survival among both groups; RR was higher in the combination arm, particularly for patients with liver metastases, and combination chemotherapy was associated with greater toxicity. Another study compared an FEC-MV (MV = methotrexate and vinblastine) combination to single-agent epirubicin followed by MV. The RR was higher for FEC-MV, but survival was the same for both groups [70].

With the emergence of the taxanes as one of the most effective classes of treatments for breast cancer, clinical trials were launched to determine the efficacy and safety of anthracycline/taxane combinations. These studies will be reviewed in more detail.

**Paclitaxel plus Anthracycline**

Many studies have reported the feasibility of combining the taxanes with doxorubicin or epirubicin. Of these, the doxorubicin/paclitaxel (AT) combinations have been studied in detail and extensive data are available regarding their clinical activity (Table 2). Early trials incorporated prolonged infusions of both drugs, but were associated with pharmacokinetic interactions between the agents which resulted in severe neurotoxicity and gastrointestinal toxicity (mucositis, typhlitis) [71-73]. The increased gastrointestinal toxicity was found to be sequence-dependent and mostly seen when paclitaxel preceded doxorubicin, secondary to delayed doxorubicin clearance [71]. Steps taken to reduce toxicity and maintain efficacy were accomplished in two ways: A) giving both agents as short infusions or bolus, or B) separating the agents to avoid pharmacokinetic interactions that lead to increased acute toxicity. Gianni and colleagues [74] reported a very high RR of 94% in one early trial utilizing bolus administration of doxorubicin (60 mg/m²) and a 3-hour infusion of paclitaxel (200 mg/m²). In this study, 20% of the patients developed

| Table 1. Efficacy of capecitabine in patients with metastatic breast cancer |
|------------------------|---------|---------|----------------|
| Author                 | n Pts.  | Dose (mg/m²) | Response rate |
| O’Shaughnessy [54]     | 62*     | 2,510      | 25%           |
| O’Reilly [55]          | 22**    | 2,510      | 35%           |
| Blum [53]              | 135***  | 2,510      | 20%           |

*Total dose = given in two divided daily doses for 14 days followed by 7 days off.

**First-line

**Anthracycline-resistant

***Anthracycline/paclitaxel-resistant
CHF. In the ECOG study that compared A versus T, versus AT the incidence of severe cardiac toxicity was no different between the doxorubicin-alone arm and the combination arm (9% versus 9%), perhaps due to the delay between the administration of doxorubicin and paclitaxel [39]. This trial did not confirm the high RR seen in earlier trials; however, it did demonstrate a superior RR and median-time-to-treatment failure for the combination compared to either single agent. Overall survival was similar for all three arms of the study.

Methods to reduce the cardiac toxicity associated with this regimen include substituting epirubicin for doxorubicin, adding dexrazoxane (a cardioprotectant) to the regimen and limiting the cumulative amount of doxorubicin administered. In the bolus combination regimens, if the cumulative dose of doxorubicin is limited to 300-360 mg/m$^2$ and the paclitaxel continued until progression, the RR is maintained and the incidence of CHF drops to about 1%-5%. [74]. In another randomized trial the AT combination (50 mg/m$^2$ day 1,220 mg/m$^2$ day 2, respectively) was shown to be superior to FAC (500 mg/m$^2$, 50 mg/m$^2$, 500 mg/m$^2$, respectively) as first-line therapy of patients with metastatic breast cancer. In this study, RR (68% versus 55%), time-to-progression (8.3 months versus 6.2 months), and overall survival (22.7 months versus 18.3 months) were significantly higher in the AT arms [75]. Trials are ongoing to investigate the role of dexrazoxane in this combination [76].

The safety and efficacy of paclitaxel in combination with epirubicin has been evaluated in several phase I and II studies [77-79]. Conte and associates [80, 81] escalated the dose of paclitaxel up to 225 mg/m$^2$ given over 3 hours in combination with epirubicin, given at 90 mg/m$^2$ as a bolus. The RR was 80%, and the regimen was well-tolerated. The most frequent dose-related toxicity was grade 4 neutropenia, which occurred in 59% of courses. The cardiac toxicity was low. Only 2 of 29 patients experienced a decrease of left ventricular ejection fraction below 50% after six courses, and no signs of anthracycline-induced CHF were noted. A phase II study conducted by the EORTC compared epirubicin plus paclitaxel (EP) with epirubicin plus cyclophosphamide (EC) as front-line therapy for patients with metastatic breast cancer. Preliminary data from this study showed that EP is as active as EC, although there was no difference in time to progression between the two groups [82].

### DOCETAXEL PLUS ANTHRACYCLINE

The combination of doxorubicin with docetaxel (ATx) is a highly active regimen for metastatic breast cancer. Docetaxel is administered over 1 hour and doxorubicin is given as either short infusions or bolus injections. High RR of 81% were reported in phase I trials of ATx at doses ranging from 40-60 mg/m$^2$ for doxorubicin and 50-85 mg/m$^2$ for docetaxel [83]. The dose-limiting toxicity with this regimen was sepsis. The recommended phase II doses were doxorubicin 50 mg/m$^2$ bolus plus docetaxel 75 mg/m$^2$ over 1 hour or doxorubicin 60 mg/m$^2$ bolus plus docetaxel 60 mg/m$^2$ over 1 hour. In a phase II study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP B-57), ATx produced an RR of 53% (PR = 47%; CR = 6%) with manageable toxicity [84]. Interestingly, an excess of cardiac toxicity was not seen with this combination, one advantage over some of the paclitaxel-doxorubicin combinations. Ongoing phase III trials comparing the ATx combination to standard regimens for metastatic and primary breast cancer will assist in determining the optimal combination chemotherapy regimen for breast cancer. One such trial is comparing ATx to the standard regimen doxorubicin plus cyclophosphamide (AC). Preliminary data indicated that ATx produced a superior RR (60% versus 47%) and longer time to progression (37.1 weeks versus 31.9 weeks), at the expense of higher hematologic toxicity [85]. Overall survival data from this study have yet to be reported.

Pagani et al. [86] recently reported a phase I-II study of docetaxel in combination with epirubicin as first-line...
chemotherapy for patients with metastatic breast cancer. Seventy patients were evaluated. The dose-limiting toxicity was neutropenia and G-CSF was required in 44% of patients. Otherwise the regimen was well-tolerated. Only one patient developed symptomatic CHF, and six additional patients had decreases in left ventricular ejection fraction with no symptoms. The RR was 66%. No pharmacokinetic interactions were observed between docetaxel and epirubicin.

**OTHER POLYCHEMOTHERAPY REGIMENS**

There is great interest in developing non-anthracycline combination regimens. The taxanes have been studied in combination with a variety of agents. Perez and collaborators [87] conducted a phase II study of paclitaxel (200 mg/m² over 3 hours) in combination with carboplatin (area under the curve 6 mg/ml per minute) administered as first-line therapy for patients with metastatic breast cancer. The main toxicity was hematologic and 16% of patients developed peripheral neuropathy. The RR was 62%. Sawada and colleagues [88] showed that both taxanes enhance the efficacy of capecitabine and 5′-dFURd in vivo, probably by modulating dThdPase activity in tumor tissues. In a human xenograft model, these authors showed a synergistic interaction between docetaxel and capecitabine. O’Saughnessy and collaborators [89] have recently completed a phase III study of docetaxel in combination with capecitabine versus single-agent docetaxel for patients with metastatic breast cancer previously exposed to anthracyclines. Preliminary data from this large randomized study indicate that the docetaxel/capecitabine combination is superior to docetaxel monotherapy in terms of RR, time to progression, and survival.

Vinorelbine has been studied in combination with other agents commonly administered for the treatment of metastatic breast cancer. Early phase II clinical trials showed high RR for a vinorelbine/doxorubicin combination [90]. However, the superiority of this combination could not be reproduced in a large randomized phase III trial conducted by the National Cancer Institute of Canada [91]. In this study, vinca alkaloid- and anthracycline-naïve patients with metastatic breast cancer were randomized to receive vinorelbine plus doxorubicin or doxorubicin alone. The RR, quality of life, and time to progression were not significantly different between the arms, suggesting that the vinorelbine/doxorubicin combination is not superior to doxorubicin as a single agent for metastatic breast cancer. Vinorelbine has been studied in combination with other chemotherapy drugs including paclitaxel, docetaxel, and 5-FU [92].

Gemcitabine is also being evaluated in combination with anthracyclines, taxanes, and vinorelbine. In general, these combinations are active but toxicities are usually additive.

In the absence of randomized trial data, the role of these combinations remains uncertain.

In summary, chemotherapy combinations produce higher RR compared with sequential single-agent therapy. The taxane/anthracycline combinations are the most effective regimens and are rapidly becoming the first-line therapy of choice for patients with metastatic breast cancer. However, the impact of polychemotherapy regimens in overall survival is modest (Table 3). Except for the commonly used two/three-drug regimens (i.e., FAC, FEC, CMF, ATx), there is little rationale to support the use of more sophisticated chemotherapy combinations.

**HIGH-DOSE CHEMOTHERAPY**

A retrospective study conducted by Hyriniuck and colleagues suggested that patients with metastatic breast cancer who had received the planned full dose of chemotherapy had a better response compared with patients who had received a less intense regimen [93]. Phase I studies showed that the dose of “standard” chemotherapy regimens could be increased by 30% to 50% using hematopoietic growth factors (e.g., G-CSF). Higher doses could be achieved using hematopoietic stem cells isolated from the bone marrow or peripheral circulation. One of the major limitations of this approach has been the extramedullary toxicity of many of the agents used for the treatment of metastatic breast cancer. Because of this limitation, most of the drugs employed for high dose-intensity regimens are restricted to alkylating agent therapy. With high-dose combination alkylating agents, overall RR between 70% to 100% can be obtained in patients with previously untreated metastatic breast cancer. More importantly, CR rates with these regimens range between 40% and 60%. However, median duration of response and survival have not been modified by high dose-intensity regimens, and while

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<td>Dox/Pac</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CMFP = cyclophosphamide, methotrexate, 5-fluorouracil, prednisone; P = prednisone; V = vincristine; E = epirubicin; Mi = mitomycin; Dox = doxorubicin; Pac = paclitaxel

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**Table 3. Phase III studies of single agent chemotherapy versus combination chemotherapy**
IHC score was 2+ or 3+. The addition of trastuzumab to scale. Tumors were considered Her-2/neu-positive if the overexpression was measured by IHC using a 0, 1+, 2+, 3+ with anthracyclines received doxorubicin (or epirubicin in treated with paclitaxel. Patients who had not been treated exposed to anthracyclines in the adjuvant setting were breast cancer were randomized to chemotherapy or chemotherapy [101, 102]. In the pivotal phase III trial of front-line therapy and in patients who had received prior mAb therapy for breast cancer is moving forward both in the experimental and clinical arenas [96]. Trastuzumab (Herceptin™; Genentech Inc.; South San Francisco, CA) is a humanized recombinant mAb directed against the anti-Her-2/neu protein. This biological therapy has been recently approved by the FDA for patients with Her-2/neu-overexpressing metastatic breast cancer. The Her-2/neu gene (also known as c-erbB-2) is amplified in 20%-30% of invasive breast carcinomas and is associated with poor prognosis. [97]. Women whose tumors overexpress Her-2/neu have a worse survival compared with patients whose tumors do not [98]. The Her-2/neu gene and protein study can be measured in formalin-fixed, paraffin-embedded tissue by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC), respectively. Pauletti and collaborators [99] showed that FISH is more specific than IHC for detecting altered Her-2 expression as a prognostic marker for breast cancer.

The Her-2/neu oncoprotein is an excellent therapeutic target because it is localized to the cell membrane; it is present in a very high proportion of cancer cells in overexpressing tumors; and overexpression at the primary tumor correlates with overexpression at distant metastatic sites [100]. Phase I studies showed that trastuzumab can be delivered safely, with reliable pharmacokinetics. The half-life of trastuzumab in the serum is 8-10 days. Phase II studies of trastuzumab reported objective responses both as front-line therapy and in patients who had received prior chemotherapy [101, 102]. In the pivotal phase III trial of trastuzumab, patients with Her-2/neu-overexpressing tumors who had not been previously treated for metastatic breast cancer were randomized to chemotherapy or chemotherapy plus trastuzumab. Patients who had been exposed to anthracyclines in the adjuvant setting were treated with paclitaxel. Patients who had not been treated with anthracyclines received doxorubicin (or epirubicin in Europe) and cyclophosphamide. In this study, Her-2/neu overexpression was measured by IHC using a 0, 1+, 2+, 3+ scale. Tumors were considered Her-2/neu-positive if the IHC score was 2+ or 3+. The addition of trastuzumab to standard chemotherapy improved RR, time to progression and survival [103, 104]. A recent analysis of over 600 specimens from breast cancer patients who participated in pivotal phase II and phase III trials of trastuzumab showed a good correlation between high Her-2/neu overexpression as measured using IHC (score 3+) and gene amplification as measured using FISH. In this retrospective study, FISH was the most precise method for predicting response to trastuzumab therapy. Patients whose tumors were FISH-negative (having no Her-2/neu gene amplification) did not appear to benefit from trastuzumab therapy regardless of their Her-2/neu status as measured using IHC. In contrast, the RR and survival rate were significantly improved in patients whose tumors were Her-2/neu-positive according to FISH [105]. These data suggest that the presence of Her-2/neu gene amplification as measured by FISH is the best predictor of response to Trastuzumab-based therapy.

Seidman et al. [106, 107] evaluated the concomitant weekly administration of paclitaxel and trastuzumab for patients with Her-2/neu-overexpressing and non-overexpressing metastatic breast cancer. The treatment was well-tolerated and cardiac events were rare. The RR was 83% for patients whose tumors overexpressed Her-2/neu as measured using the mAb TAB-250. Patients whose tumors were Her-2/neu-negative as measured by the same antibody had a 45% RR. In this study, mAb (TAB-250 and CB11) and FISH were better predictors of response than polyclonal antibodies (HercepTest, PAB1). A phase III study (Cancer and Leukemia Group B 98-40) that is evaluating the role of weekly paclitaxel versus the standard 3-weekly schedule has been amended to incorporate trastuzumab for all Her-2/neu-positive patients. Patients whose tumors do not overexpress Her-2/neu may or may not be randomized to trastuzumab.

Burstein and colleagues [66] studied a weekly regimen of trastuzumab and vinorelbine for patients with Her-2/neu-overexpressing metastatic breast cancer. The overall RR in 34 evaluable patients was 75%. For patients who received this combination as first-line therapy the RR was 84%. Interestingly, the RR was significant even if patients had been exposed to anthracyclines (RR = 88%), a taxane (RR = 50%), or both drugs (RR = 73%). These results suggest that there may be a true synergistic interaction between vinorelbine and trastuzumab that may have clinical application. The combination of vinorelbine and trastuzumab was well-tolerated in this small phase II trial. Cardiac toxicity was reported in two patients, but was asymptomatic, with less than a 20% decrease in left ventricular ejection fraction.

Ongoing clinical trials are exploring the role of trastuzumab in combination with other chemotherapy drugs including cisplatin, carboplatin, docetaxel, gemcitabine, and capecitabine [108]. Strategies to reduce cardiac toxicity
associated with anthracycline plus trastuzumab combinations include concomitant use of cardioprotectant agents (e.g., Zinecard) and use of liposomal doxorubicin formulations (e.g., Doxil, TLC-D99).

### PROMISING NEW AGENTS

The development of novel anticancer agents continues on several fronts. One approach is to develop analogues of older drugs with improved efficacy and/or safety profiles. Examples include novel anthracyclines (e.g., annamycin), novel formulations (e.g., liposomal doxorubicin), water-soluble taxanes, and new oral fluoropyrimidines. A second approach is to study agents that belong to classes of compounds that historically have had little activity against breast cancer cells. These include gemcitabine and topoisomerase I inhibitors (e.g., DX8951f, RFS-200). A third strategy is to interfere with mechanisms of drug resistance using inhibitors of the multidrug resistance pump. There are over 300 new compounds in development in oncology today, and a good percentage of them represent cytotoxic drugs (Table 4).

In addition to cytotoxic chemotherapy, there is great interest in developing novel molecular-based therapeutics targeted at inhibition of tumor cell proliferation pathways. Promising targets include growth factor receptors and their ligands, intracellular signal transduction molecules, cell-cycle regulatory proteins, and transcription factors (Table 5).

### Table 4. Novel cytotoxic agents in breast cancer

<table>
<thead>
<tr>
<th>Alkylating agents</th>
<th>Bendamustine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>AD-198, 14-Acyl-N-benzyl anthracyclines</td>
</tr>
<tr>
<td>Anthrapyrazoles</td>
<td></td>
</tr>
<tr>
<td>Antifols</td>
<td>LY231514 (MTA), LY309887</td>
</tr>
<tr>
<td></td>
<td>Ralitrexed (Tomudex)</td>
</tr>
<tr>
<td></td>
<td>γ-Methylene-10-Deaza-aminopterin (MDAM)</td>
</tr>
<tr>
<td>Camptothecins</td>
<td>DX8951f, RS200</td>
</tr>
<tr>
<td>Fluoropyrimidines</td>
<td></td>
</tr>
<tr>
<td>Nucleoside analogues</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Taxanes</td>
<td></td>
</tr>
<tr>
<td>Alkylphosphocholines</td>
<td>Mifeleosine, Perifosine</td>
</tr>
<tr>
<td>Aminoacridines</td>
<td>CT-2584</td>
</tr>
<tr>
<td>Declopamide</td>
<td></td>
</tr>
<tr>
<td>Depsipptide (FR901228)</td>
<td></td>
</tr>
<tr>
<td>Diarylsulfonylureas</td>
<td></td>
</tr>
<tr>
<td>Diethylspermine</td>
<td></td>
</tr>
<tr>
<td>Epigallocatechin</td>
<td></td>
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<tr>
<td>Epothilones</td>
<td></td>
</tr>
<tr>
<td>Indolocarbazoles</td>
<td></td>
</tr>
<tr>
<td>6-Hydroxymethylacyl-fulvene</td>
<td></td>
</tr>
<tr>
<td>Microtubule inhibitors</td>
<td>T138067-sodium</td>
</tr>
<tr>
<td>Pectin derivatives</td>
<td>GBC-590</td>
</tr>
<tr>
<td>Rebeccamycin analogue (NSC 655649)</td>
<td></td>
</tr>
<tr>
<td>Sulfonated Distamycin A analogues</td>
<td></td>
</tr>
<tr>
<td>Spicamycin (KRN5500)</td>
<td></td>
</tr>
<tr>
<td>Substituted dihydro-benzoxazine (FK317)</td>
<td></td>
</tr>
<tr>
<td>TAS-103</td>
<td></td>
</tr>
<tr>
<td>Temozolamide Tetrahydroisoquinol alkaloids</td>
<td>Eteineascidin-743</td>
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<td></td>
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</tbody>
</table>

### Table 5. Novel noncytotoxic agents in breast cancer

<table>
<thead>
<tr>
<th>Target/Mechanism of Action</th>
<th>Strategy or Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Her-2/neu</td>
<td>Trastuzumab (Herceptin®)</td>
</tr>
<tr>
<td></td>
<td>Bispecific mAb</td>
</tr>
<tr>
<td></td>
<td>E23(Fv)PE</td>
</tr>
<tr>
<td></td>
<td>E1A gene therapy</td>
</tr>
<tr>
<td></td>
<td>E75 peptide vaccine</td>
</tr>
<tr>
<td>EGFR</td>
<td>C225 mAb</td>
</tr>
<tr>
<td></td>
<td>Tyrosine kinase inhibitors</td>
</tr>
<tr>
<td>Protein Kinase C inhibitors</td>
<td>Bryostatin</td>
</tr>
<tr>
<td></td>
<td>Miltefosine</td>
</tr>
<tr>
<td>Farnesyl transferase inhibitors</td>
<td>Antisense Therapy</td>
</tr>
<tr>
<td>BCL-2</td>
<td>TNP-470</td>
</tr>
<tr>
<td></td>
<td>Neovastatin</td>
</tr>
<tr>
<td></td>
<td>Angiostatin</td>
</tr>
<tr>
<td></td>
<td>Endostatin</td>
</tr>
<tr>
<td></td>
<td>CM101 (endotoxin)</td>
</tr>
<tr>
<td></td>
<td>Interferon alpha</td>
</tr>
<tr>
<td></td>
<td>Interleukin 12</td>
</tr>
<tr>
<td></td>
<td>RFP4</td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
</tr>
<tr>
<td></td>
<td>Ribozyme Therapy</td>
</tr>
<tr>
<td></td>
<td>rHuVEGF antibody</td>
</tr>
<tr>
<td>Matrix Metalloproteinase inhibitors</td>
<td>Marimastat</td>
</tr>
</tbody>
</table>

Abbreviations: EGFR = epidermal growth factor receptor; rHu = recombinant human; VEGF = vascular endothelial growth factor.
These agents are not likely to produce CR in patients with metastatic solid tumors and it will be critical to combine them with chemotherapy in order to affect maximal tumor reduction [109].

CONCLUSION
The role of chemotherapy is well-established for patients with estrogen receptor-negative and hormone-refractory breast cancer. Although polychemotherapy regimens produce higher RR compared with single-agent therapy, the survival impact is modest. Anthracycline plus taxane regimens are the most effective therapy, at the price of higher toxicity, and should be considered for patients with rapidly growing visceral metastases, lymphangitic spread, or locally advanced breast cancer. For the majority of patients, the available data support the sequential use of single-agent chemotherapy or the usual two- to three-drug combination regimens (e.g., FAC, FEC, CMF). It is likely that well-tolerated novel combinations will replace older regimens. Marked progress has been made to make chemotherapy more tolerable using more effective antiemetics, antibiotics, and hematopoietic growth factors. Development of novel therapeutic agents continues, based on expanded biological understanding of tumor development and progression. Antiangiogenic therapy and signal transduction inhibitors are the biologic agents most likely to be combined with chemotherapy in the near term.

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