

Recent Advances in the Systemic Therapy of Breast Cancer

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A number of advances have been made over the last decade in the systemic therapy of breast cancer, including 1) the introduction of the taxanes, paclitaxel and docetaxel, into the treatment regimes for both early and advanced breast cancer; 2) a greater understanding of the use of high-dose chemotherapy, supplemented with stem cell rescue; 3) the development of newer parenteral and oral chemotherapeutic drugs; 4) the first biologic therapy for breast cancer; 5) the first demonstration of effective drug therapy to prevent the development of breast cancer; and 6) effective agents to palliate and/or prevent complications from bone metastasis. These and other developments are allowing both the extension of life and a better quality of life for those stricken with the breast cancer.

Cole JT. Recent advances in the systemic therapy of breast cancer. The Ochsner Journal 2000; 2:24-32.

Introduction

The last decade of the 20th century will be remembered for a number of exciting developments in the systemic therapy of breast cancer. Major strides have been taken in our ability to treat patients, from the development of new chemotherapeutic and hormonal agents for the treatment of advanced disease to innovations in the adjuvant treatment of early breast cancer, including the introduction of new agents and the evaluation and modification of chemotherapy dosages. In addition to the increasing array of new chemotherapy drugs, we have witnessed the development of the first targeted biologic treatment of breast cancer, which, hopefully, presages the arrival of other nontraditional drug therapies. Several of these newer therapies are, or soon will be, undergoing clinical trials, while new advances in the realm of supportive care are improving the quality of life of breast cancer patients.

Taxanes

The drugs that have been associated with the greatest excitement and expectations in breast cancer treatment have been the taxanes: paclitaxel (Taxol; Bristol-Meyers Squibb, Princeton, NJ) and docetaxel (Taxotere; Rhone-Poulenc Rorer

Antony, France). These complex antineoplastic agents, derived from the bark or needles of the yew tree (1), act by binding to the microtubules of cells and enhancing microtubular assembly (2). This ultimately leads to G₂ and M phase blockade, which is lethal (3).

Paclitaxel

Paclitaxel (P) was the first of the taxanes to be used extensively. Holmes et al (4) administered P to 25 patients who had previously been treated with chemotherapy. A response rate of 56% was obtained using a dose of 250 mg/m² by continuous infusion over 24 hours with neutropenia as the dose-limiting toxicity. Reichman et al (5) used a similar schedule and dose, combined with granulocyte colony stimulating factor (G-CSF) to limit neutropenia, to reach a 62% response rate in previously untreated patients. A large Canadian and European study (6) compared a 3-hour infusion schedule of either 135 mg/m² or 175 mg/m². Seventy percent of those studied had previously received chemotherapy treatment. At the higher dose level, 29% responded to treatment compared with 22% at the lower dose level. Based on this trial, 175 mg/m² is the most commonly

used dose for P, which appears to be active in patients previously treated with anthracyclines (7), making it an important drug for patients who previously had few choices for second-line therapy. Dose intensification of P given as a short infusion does not seem to improve efficacy (8); however, there are data that suggest longer infusion times may lead to higher response rates (9).

Docetaxel

Docetaxel is a semisynthetic taxane that has demonstrated activity in metastatic breast cancer patients who have previously received chemotherapy. In a phase II study for the European Organization for Research and Treatment of Cancer (EORTC), Chevallier et al (10) reported that 68% of assessable patients responded to a docetaxel dosage of 100 mg/m² given over 1 hour every 3 weeks. Like P, docetaxel is also active in patients previously treated with anthracyclines.

Ravdin et al (11) demonstrated a docetaxel response rate of 57% (20/35) in a group of patients resistant to doxorubicin (D) or mitoxantrone. The most frequently encountered toxicities have included often-severe neutropenia, neurosensory changes, asthenia, stomatitis, and skin changes. Fluid retention has also been noted in some patients; however, these effects have largely been eliminated with dexamethasone therapy in the peri-treatment period (12).

Several groups have recently demonstrated that the toxicity associated with taxane therapy could be improved, while preserving anti-tumor efficacy, by using a weekly schedule. Seidman et al (13) treated 30 patients at Memorial Sloan-Kettering with a weekly P dose of 100 mg/m² to reach an overall response rate of 53% accompanied by little acute or chronic myelosuppression. The major toxicity was peripheral neuropathy. Weekly docetaxel doses of 36 mg/m² to 40 mg/m² per week produce similar response rates of approximately 50% with side effects consisting of neutropenia, asthenia, neuropathy, and fluid retention (14,15).

Combination Taxane Therapy

The excellent single-agent activity of the taxanes has generated enthusiasm for the development of combination chemotherapy using taxanes and other drugs active against advanced breast cancer. Gianni et al (16), of the National Cancer Institute-Milan, demonstrated response rates of up to 94% in chemotherapy-naïve patients (n=35) with a combination of P and D, including 41% complete responses. Of the total group treated, 18% developed reversible congestive heart failure. Modest neuropathy was the other major side effect.

A large randomized Intergroup trial of 739 patients demonstrated a 46% response rate for the combination of P and D with no excess cardiac toxicity (17). Those treated with a single agent D or P demonstrated inferior response rates of 34% and 33%, respectively ($p = .007$ D vs DP; $p = .004$ P vs DP). There was no difference in survival, perhaps due to the crossover feature of this protocol, which allowed patients progressing on one single agent to cross over to the other. Combinations of P and other anthracyclines, such as epidoxorubicin, have also produced excellent response rates (18).

Comparative Taxane Responses

Taxanes have shown significant activity compared with other standard chemotherapies. Bishop et al (19) compared P to the cyclophosphamide (C) methotrexate (M), 5 fluorouracil (F), and P combination (CMFP) in a randomized trial involving 209 patients, none of whom had been previously treated with chemotherapy for metastatic disease. Treatment with P alone demonstrated significantly longer median survival (17.3 months) compared with CMFP (13.9 months; $p = 0.025$).

In another phase III trial (20), docetaxel (100mg/m²) was compared with intensive single-agent D (75 mg/m²), both administered every 3 weeks. Docetaxel produced a significantly higher response rate (47.8% vs 33.3%; $p = 0.008$) with lower toxicity but no difference in survival.

Docetaxel has been compared with the combination of mitomycin C and vinblastine in metastatic breast cancer patients who failed prior anthracycline therapy. A significant survival advantage was seen in the docetaxel-treated patients (docetaxel 11.4 months, mitomycin C and vinblastine 8.7 months; $p = 0.0097$) (21).

Adjuvant Use of Taxanes

Taxane activity in anthracycline-resistant cancers has led to several large adjuvant trial evaluations in the United States. The first to be reported was the 1998 Intergroup trial (22), which postoperatively compared four cycles of Adriamycin (A; doxorubicin, Pharmacia and Upjohn, Kalamazoo, MI) and C to four cycles of the same drugs followed by four cycles of P (estrogen receptor-positive women were also treated with tamoxifen [T] and all patients had positive axillary lymph nodes). The results demonstrated a significant recurrence-free survival advantage for those patients receiving P (ACP 90% vs AC 86%; $p = 0.0077$). There was also a small but significant overall survival advantage for the P-treated group (97% vs 95% for controls; $p = 0.0390$). Interestingly, on subset analysis,

only the hormone receptor-negative patients seemed to benefit from the addition of P therapy.

The second large trial investigating the addition of taxane therapy to the standard postoperative AC therapy is the on-going National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-28 comparing four cycles of AC with ACP. Accrual was completed in May 1998 with 3060 patients entered. The results of this study should solidify our understanding of the addition of taxanes to standard postoperative chemotherapy. In addition, NSABP B-27 is currently investigating taxane use in patients with early breast cancer by randomizing patients to four cycles of preoperative AC (A 60 mg/m² plus C 600 mg/m²) or four cycles of preoperative AC followed by four cycles of either preoperative or postoperative docetaxel (100 mg/m²).

Adjuvant Therapy Developments

Several recently reported trials have added to our understanding of the treatment of node-negative breast cancer patients. NSABP B-20 (23) investigated the addition of certain combination chemotherapies to T therapy in node-negative estrogen receptor-positive patients. Patients were randomized to T alone, MFT, or CMFT. At 7-year mean follow-up, combination chemotherapies demonstrated a small but significant advantage in disease-free survival (T 79 %, MFT 85 %, $p=0.01$; CMFT 85 %, $p < 0.003$), as well as an overall survival (T 91%, MFT 94%, $p=0.05$; CMFT 94%, $p=0.10$).

Hutchins et al (24) evaluated adjuvant therapy for 2691 node-negative patients with high-risk (defined as tumors >2 cm in diameter, estrogen receptor and progesterone receptor-negative, or those with high s-phase fraction) node-negative breast cancer. Patients were randomized to CMF or CAF (T was also given to hormone receptor-positive patients). Those treated with CAF had a marginal improvement in disease-free survival (87% vs 82%) and overall survival (93% vs 90%; $p = 0.03$) but experienced greater toxicity in the form of granulocytopenia, nausea, vomiting, stomatitis, and alopecia.

New Agents

Vinorelbine

Vinorelbine (Navelbine; Burroughs Wellcome Co., Research Triangle Park, NC) is a semi-synthetic vinca alkaloid, which acts by causing depolymerization of the mitotic microtubular assembly (25). Fumoleau et al (26) reported a response rate of 41%, with 7% complete responses, using vinorelbine (30 mg/m² per week) as a single agent in 145 previously untreated patients. Weber et al (27) reported a 34%

overall response rate in a large nonrandomized trial involving 107 patients in 1995 with no difference between those receiving vinorelbine as first- or second-line therapy. The dose-limiting toxicity in vinorelbine studies has been granulocytopenia.

Using the combination of vinorelbine and D as initial therapy in 89 patients, Spielman et al reported a significant 74% response rate, with 21% complete responses (28). Neutropenia was the dose-limiting toxicity; neurotoxicity has generally been mild. A multicenter trial of the vinorelbine and D combination reported a 54% response rate (29).

Combinations of vinorelbine and mitoxantrone or epirubicin (E) also appear to be active (30,31), and vinorelbine plus mitomycin C has been used in several different schedules. Scheithauer et al treated 34 patients with vinorelbine plus mitomycin C and reached a 35% response rate (32). Using a more intense weekly schedule of vinorelbine plus mitomycin C every 4-6 weeks, Kardinal et al reported a 44% response rate in a group of anthracycline refractory patients at Ochsner Clinic (33). This well-tolerated combination is associated with phlebitis as well as self-limited and brief neutropenia.

Capecitabine

Capecitabine (Xeloda; Roche Laboratories, Nutley, NJ), an orally administered tumor-activated fluoropyrimidine, has demonstrated activity even in heavily pretreated patients. Blum et al reported a 20% response in P-refractory patients (34). In a randomized trial of first-line therapy for metastatic breast cancer, O'Shaughnessy et al reported a 25% response rate with capecitabine vs a 16% response rate with CMF in 95 women ≥ 55 years of age (35).

Gemcitabine

Gemcitabine, a nucleoside analogue, has demonstrated response rates of up to 25% against advanced breast cancer, with limited numbers of patients treated (36).

High-Dose Chemotherapy and Autologous Stem Cell Transplantation

In the chemotherapy of metastatic breast cancer, dose intensity has significant influence on response rate and survival (37). Based on the generally steep dose-response curves in animal models for many chemotherapeutic drugs, it has been hypothesized that increasingly higher doses should produce higher response rates and improvement in survival for advanced breast cancer patients. The use of autologous stem cell rescue has allowed this hypothesis to be tested.

Multiple regimens of alkylating agents have been employed due to their steep dose-response curves and differing nonhematological toxicities (38). Peters et al (39) reported a 54% complete response rate using high-dose C, cisplatin, and carmustine or melphalan. Similar results were reported by Williams et al (40), who found a median survival of 13.3 months in their group of 59 patients. Most importantly, early trials reported that some complete responders remained in remission for extended periods of time (41). The majority of these initial trials used bone marrow as the source of stem cells, while recent trials have favored peripheral blood stem cell sources due to more rapid reconstitution of the marrow and greater ease of procurement (42-44). The isolation of peripheral blood progenitor cells has also been explored (45,46).

The use of high-dose chemotherapy has also been investigated in the high-risk adjuvant setting. Peters et al (47) treated 85 patients with stage IIA to IIIB breast cancer, all of whom underwent resection of the primary tumor and axillary node dissection. All patients had ≥ 10 involved nodes. Actuarial event-free survival at 2.5 years was 72% compared with between 38% and 52% in historical controls receiving standard chemotherapy.

Because of the promising results from these early and largely single institution trials, several multi-institutional randomized trials of high-dose chemotherapy for metastatic disease have been performed. In the Philadelphia Intergroup Study (48), patients who responded to four to six cycles of CMF or CAF induction were randomized to conventional CMF maintenance or high-dose chemotherapy utilizing the STAMP V regimen (C 1500 mg/m²/d, thiotepa 125 mg/m²/d, and carboplatin 200 mg/m² by continuous infusion for 4 days). A total of 553 patients (199 were randomized) received induction therapy, with 303 (54%) responding. No difference was detected in overall survival between the CMF and STAMP V groups, even when the most favorable subgroup of complete responders was separately analyzed.

Three randomized trials have been reported using high-dose chemotherapy and stem cell transplant to treat high-risk surgically treated breast cancer. Bezwoda et al (49) of South Africa randomized 154 high-risk patients (defined as tumor stage T1-3a with >10 nodes involved or tumors >5 cm with seven to nine positive nodes) using C (4.4 gm/m²), mitoxantrone (45 mg/m²), and etoposide (1.5 gm/m²) as the high-dose regimen. Patients were randomly assigned to two cycles of high-dose therapy separated by 6 weeks or to six cycles of CAF (C 600 mg/m², A 50 mg/m² [or epiadriamycin 70 mg/m²], F 600 mg/m²) once every 3 weeks. At a median

follow-up of 278 weeks, 25% (19/75) of patients treated on the high-dose arm had relapsed compared with 65% (52/79) on the standard chemotherapy arm, a highly significant difference ($p < 0.001$). The high-dose group also had a significant survival advantage.

In a large North American Intergroup study of 874 women with stage II or IIA breast cancer and 10 or more involved nodes, Peters et al administered standard CAF adjuvant chemotherapy (C 600 mg/m², A 60 mg/m², and F 1200 mg/m²) every 28 days for 4 cycles (50). Patients were then randomized to either high-dose treatment (C 5625 mg/m², cisplatin 165 mg/m², and bis chloronitrosurea 600 mg/m²) with bone marrow and peripheral stem cell support or intermediate-dose therapy (C 900 mg/m², cisplatin 90 mg/m², and BCNU 90 mg/m²) with G-CSF support. All patients received local-regional radiation, and those who were hormone receptor-positive received T. At 37-month median follow-up, event-free survival was 68% for the high-dose group vs 64% for the intermediate-dose group ($p = 0.7$) with overall survival at 78% (high) vs 80% (intermediate) ($p = 0.1$), indicating no advantage for the high-dose arm.

The Scandinavian Breast Cancer Study Group 9401 (51) has also failed to show a benefit for high-dose chemotherapy. High-risk patients ($>70\%$ risk of recurrence within 5 years with conventional adjuvant treatment, using population based cohorts) were randomized to high-dose chemotherapy treatment (three courses of F [300 mg/m² to 600 mg/m²], E [38 mg/m² to 120 mg/m²], and C [450 mg/m² to 1800 mg/m²], followed by C 6 g/m², thiotepa 0.5 g/m², and carboplatin 0.8 g/m²) with peripheral blood stem cell transplant or standard chemotherapy. The standard arm used nine courses of individually tailored FEC based on leukocyte counts. Full details of this study, which represents an unorthodox approach in both the dosing schedule and the number of cycles administered, have not yet been published.

Dose-Intensive Adjuvant Chemotherapy

The issue of dose intensity has also been investigated in the development of adjuvant chemotherapy programs not requiring marrow and/or stem cell support.

The concept of a dose intensity threshold requirement has been supported by the results of a Cancer and Leukemia Group B (CALGB) study that randomized women with primary node-positive breast cancer to three dose levels of CAF (52). Patients who received the intermediate- or high-dose levels had superior disease-free survival ($p < 0.001$) and overall survival ($p = 0.004$) compared with the low-dose group.

However, it may not be useful to further escalate chemotherapy dosing in the nontransplant setting. Henderson et al (22) found no benefit to raising the dose of A from 60 mg/m² to 75 mg/m² or 90 mg/m². The NSABP has also explored the concept of dose escalation in the adjuvant setting by increasing the dose of C in the AC regimen. In protocols B-22 and B-25, the dose of C was quadrupled (from 600 mg/m² to 2400 mg/m²) and given in several schedules but the more intensive approach failed to demonstrate an advantage (53,54).

Monoclonal Antibody Therapy

Approximately 20% of breast cancers demonstrate an overexpression of the HER2 gene product, a transmembrane protein that has tyrosine kinase activity (55,56). Subsequently, trastuzumab (anti-p185 HER2 monoclonal antibody; Herceptin, Genentech, South San Francisco, CA), a chimeric mouse-human HER2 protein antibody, was developed (57). Preclinical work by Baselga et al (58) found that antibodies to this protein product could inhibit breast cancer cell growth in vitro and enhance the cytotoxic effects of P. In a phase II study, trastuzumab was shown to have low toxicity and responses were seen in some patients with advanced breast cancer (5/43, overall response 11.6%) (59).

Two important trials were subsequently conducted in patients who demonstrated overexpression of the HER2 protein. In an open label trial reported by Cobleigh et al (60), the antibody alone was given to advanced breast cancer patients who had failed standard chemotherapy. Women who overexpressed HER2 (n=222) received weekly antibody therapy and reached a 21% response rate (4% complete response, 17% partial response). Some patients experienced a reduction in cardiac function; otherwise, treatment was well tolerated.

In a trial reported by Slaman et al (61), chemotherapy-naïve advanced breast cancer patients were randomized to receive chemotherapy with either P or AC, with or without the HER2 antibody. Patients treated with chemotherapy and antibody therapy showed higher response rates compared with those treated with chemotherapy alone (25% P vs 57% P plus trastuzumab; 42% AC vs 64% AC plus trastuzumab). An unexpected finding was an increased risk of cardiac effects and myelosuppression in patients receiving concomitant antibody therapy: 18% of those receiving AC plus trastuzumab developed grade III (out of IV) cardiac dysfunction compared with 3% of those receiving AC alone, 0% for P alone, and 2% for those receiving P plus the antibody).

The weekly combination of trastuzumab and P has recently been studied by Fornier et al (62) who reported a 71% response in HER2-positive patients (20/28), while only 37.5% of the HER2-negative patients responded. Several adjuvant trials currently underway should help to further define the role of trastuzumab in the treatment of early breast cancer.

Hormonal Agents

Tamoxifen and Raloxifene

Tamoxifen is the most widely used hormonal agent in the treatment of breast cancer. It has been useful in the treatment of advanced hormonally responsive breast cancer and in the postoperative adjuvant setting for estrogen receptor-positive patients. Since estrogen exposure is related to breast cancer development, it was postulated T might be able to prevent the development of breast cancer by interfering with estrogen's stimulation of breast tissue. To answer this question, the NSABP performed the P-1 Trial (63) involving 13,388 women at an increased risk of developing breast cancer based on a statistical model. Half received T while the other half received placebo. T use was associated with a 49% reduction in the risk of developing invasive breast cancer and a 50% reduction in noninvasive breast cancer. With the completion of the P-1 Trial, the era of chemoprevention is now upon us.

Raloxifene (Evista, Eli Lilly, Indianapolis, IN) is a newer selective estrogen receptor modulator that has been approved in the United States for use as a preventative treatment for osteoporosis. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial studying osteoporosis (64), a significant reduction in the risk of breast cancer was found in 7704 postmenopausal women randomized to raloxifene or placebo (21% of raloxifene-treated women developed breast cancer compared with 0.82% placebo; relative risk = 0.26). The relative efficacy of T and raloxifene in the prevention of breast cancer is currently being tested by the NSABP in the Study of Tamoxifen and Raloxifene (STAR) trial. Postmenopausal women with a threshold risk of breast cancer as defined by the Gail Model (65) will be randomized to T (20 mg/d) or raloxifene (60 mg/d). Planned enrollment is 20,000.

The use of T in the treatment of noninvasive breast cancer was investigated in NSABP B-24 (66), which randomized 1804 women with resected noninvasive breast cancer to T or placebo. There were 31% fewer noninvasive breast cancer events in the T-treated group, as well as a 43% reduction in the development of invasive breast cancers compared with placebo (41 events vs 70 events, respectively; absolute difference 3.1% at 5 years).

Aromatase Inhibitors

The aromatase inhibitors anastrozole (Arimidex, Zeneca Pharmaceuticals, Wilmington, DE) and letrozole inhibit the production of estrogens from adrenal precursors and are useful second-line hormonal therapies for patients for whom anti-estrogen therapy is unsuccessful. In a randomized trial of 551 patients, Dombrowsky et al (67) found that letrozole (2.5 mg daily) produced a significantly higher response rate of 24% compared with megestrol acetate (160 mg/d; response rate 16%). Letrozole was also better tolerated, with fewer cardiovascular side effects and less weight gain. Trials comparing anastrozole and megestrol acetate have demonstrated response rates but anastrozole has demonstrated fewer side effects (68). Anastrozole and letrozole have largely replaced megestrol for second-line hormonal therapy due to their superior or equivalent activity and favorable side effect profiles.

Biphosphonates

Skeletal metastases are a frequent cause of morbidity in advanced breast cancer patients, due primarily to osteolytic metastasis (69). Bisphosphonates inhibit the activity of osteoclasts, which mediate metastatic bone disease, and have been successfully used to treat breast cancer patients with bone metastases.

Paterson et al (70) compared clodronate with placebo in a study of 173 patients with osteolytic bone metastasis demonstrating reductions in bone pain as well as pathologic fractures in the treated group. Van Holten-Verzantvoort (71) demonstrated similar results with oral pamidronate (300 mg/d) vs placebo. In two randomized trials of patients with osteolytic bone metastasis (n = 751), Hortobagyi et al (72) administered intravenous pamidronate (90 mg over 2 hours once a month) demonstrating a decrease in both skeletal complications (p = 0.0001) and bone pain. Interestingly, those patients who received concomitant chemotherapy seemed to derive the greatest benefit, raising the question of a possible synergistic effect between the two types of therapy.

Summary

We are still in the midst of developing a more complete understanding of how best to use the unprecedented selection of new options for the systemic therapy of breast cancer. Some new agents are finding their way into the therapeutic schemata for adjuvant therapy, and taxanes are now a part of standard treatment for many patients. Current clinical trials using trastuzumab antibody therapy in the adjuvant setting give us increased hope for a greater ability to cure and great excitement for a future where less toxic and more effective therapies are available.

Abbreviation Guide

A = Adriamycin (A; doxorubicin, Pharmacia and Upjohn, Kalamazoo, MI)
 C = cyclophosphamide
 D = doxorubicin
 E = epirubicin
 F = 5 fluorouracil
 M = methotrexate
 P = paclitaxel
 T = tamoxifen

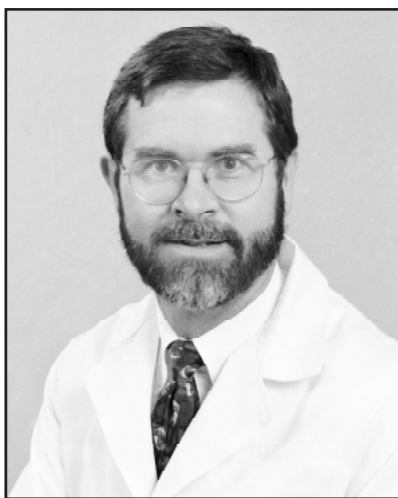
References

1. Gelmon K. The Taxoids: Paclitaxel and docetaxel. *Lancet* 1994; 344:1267-1272.
2. Horowitz SB. Mechanism of action of taxol. *Trends Pharmacol Sci* 1992; 13:134-136.
3. Fromes Y, Gounon P, Bissery MC, et al. Differential effects of taxol or taxotere on TAU and MAP2 containing microtubules. *Proc Am Assoc Cancer Res* 1992; 33:551.
4. Holmes FA, Walters RS, Theriault RL, et al. Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. *J Natl Cancer Inst* 1991; 83:1797-1805.
5. Reichman BS, Seidman AD, Crown JPA, et al. Paclitaxel and recombinant granulocyte colony – stimulating factor as initial chemotherapy for metastatic breast cancer. *J Clin Oncol* 1993; 11:1943-1951.
6. Nabholz JM, Gelman K, Bouterbal M, et al. Randomized trial of two doses of taxol in metastatic breast cancer: an interim analysis. *Proc Am Soc Clin Oncol* 1993; 12:60.
7. Seidman A, Crown J, Reichman B, et al. Lack of cross resistance of taxol with anthracycline in the treatment of metastatic breast cancer. *Proc Am Soc Clin Oncol* 1993; 12:63.
8. Winer E, Berry D, Duggan D, et al. Failure of higher dose paclitaxel to improve outcome in patients with metastatic breast cancer – results from CALGB 9342. *Proc Am Soc Clin Oncol* 1998; 17:388A.
9. Mamounas E, Brown A, Smith R, et al. Effect of taxol duration of infusion in advanced breast cancer: Results from NSABP B-26 trial comparing 3 to 24 hour infusion of high dose Taxol. *Proc Am Soc Clin Oncol* 1998; 17:389A.
10. Chevallier B, Fumoleau P, Kerbrat P, et al. Docetaxel is a major cytotoxic drug for the treatment of advanced breast cancer: A phase II trial of the Clinical Screening Cooperative Group of the European Organization for Research and Treatment of Cancer. *J Clin Oncol* 1995; 13:314-322.
11. Ravdin PM, Burris HA III, Cook G, et al. Phase II trial of docetaxel in advanced anthracycline-resistant or anthracenedione resistant breast cancer. *J Clin Oncol* 1995; 13:2879-2885.

12. Trudeau ME, Eisenhauer EA, Higgins BP, et al. Docetaxel in patients with metastatic breast cancer: a phase II study of the National Cancer Institute of Canada – Clinical Trials Group. *J Clin Oncol* 1996; 14:422-428.
13. Seidman AD, Hudis CA, Albanel J, et al. Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol* 1998; 16:3353-3361.
14. Loffler TM, Freund W, Droge C, et al. Activity of weekly taxotere in patients with metastatic breast cancer. *Proc Am Soc Clin Oncol* 1998; 17:435A.
15. Hainsworth JD, Burris HA III, Erland JB, et al. Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. *J Clin Oncol* 1998; 16:2164-2168.
16. Gianni L, Munzone E, Capri G, et al. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: High antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J Clin Oncol* 1995; 13:2688-2699.
17. Sledge GW, Jr, Neuberger D, Ingle J, et al. Phase III trial of doxorubicin vs paclitaxel vs doxorubicin plus paclitaxel as first line therapy for metastatic breast cancer: an Intergroup trial. *Proc Am Soc Clin Oncol* 1997; 16:2A.
18. Alabiso O, Durando A, Malossi A, et al. Paclitaxel and epidoxorubicin as first line therapy in metastatic breast cancer A phase I-II study. *Proc Am Soc Clin Oncol* 1998; 17:479A.
19. Bishop JF, Dewar J, Toner, GC, et al. Initial paclitaxel improves outcome compared to CMFP combination chemotherapy or front-line therapy in untreated metastatic breast cancer. *J Clin Oncol* 1999; 17:2355-2364.
20. Chan S, Friedrichs K, Noel D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 1999; 17:2348-2354.
21. Nabholz JM, Thuerlimann B, Beswoda WR, et al. Taxotere improves survival over mitomycin C, vinblastine in patients with metastatic breast cancer who have failed an anthracycline containing regimen: Final result of a phase III randomized trial. *Proc Am Soc Clin Oncol* 1998; 17:390A.
22. Henderson IC, Berry D, Demetri G, et al. Improved disease-free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (PTS) with node positive primary breast cancer. *Proc Am Soc Clin Oncol* 1998; 17:390A.
23. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen and chemotherapy for lymph node negative, estrogen receptor – positive breast cancer. *J Natl Cancer Inst* 1997; 89:1673-1682.
24. Hutchins L, Green S, Ravdin P. CMF vs CAF with and without tamoxifen in high risk node negative patients and a natural history follow-up study in low risk node negative patients: First results of intergroup trial 0102. *Proc Am Soc Clin Oncol* 1998; 17:2A.
25. Langlois N, Gueritte F, Langlois Y, et al. Application of a modification of the Polonovski reaction to the synthesis of vinblastine-type alkaloids. *J Am Chem Soc* 1976; 98:7017-7024.
26. Fumoleau P, Delgado FM, Delozier T, et al. Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol* 1993; 11:1245-1252.
27. Weber BL, Vogel C, Jones S, et al. Intravenous vinorelbine as first-line and second-line therapy in advanced breast cancer. *J Clin Oncol* 1995; 13:2722-2730.
28. Spielmann M, Dorval T, Turpin F, et al. Phase II trial of vinorelbine/doxorubicin as first-line therapy of advanced breast cancer. *J Clin Oncol* 1994; 12:1764-1770.
29. Hochster H, Vogel C, Blumenreich JG, et al. A multicenter phase II study of navelbine and doxorubicin as first line, chemotherapy of metastatic breast cancer. *Proc Am Soc Clin Oncol* 1994; 13:100.
30. Chadja M, Izzo J, May-Levin F, et al. Preliminary data on 4 epidriamycin – vinorelbine: a new active combination in advanced breast cancer (abstract). *Proc Am Soc Clin Oncol* 1993; 12:88.
31. Ferrero JM, Wemding JL, Hoch M, et al. Mitoxantrone – vinorelbine as first line chemotherapy in metastatic breast cancer: a pilot study. *Proc Am Soc Clin Oncol* 1993; 12:108 (abstract).
32. Scheithauer W, Kornek G, Haider K, et al. Effective second line chemotherapy in advanced breast cancer with navelbine and mitomycin C. *Breast Cancer Res Treat* 1993; 26:49-53.
33. Kardinal CG, Cole JT, Gralla RJ, et al. Navelbine (vinorelbine) and mitomycin C: Combination therapy in advanced breast cancer. *Proc Am Soc Clin Oncol* 1995; 14:131A.
34. Blum JL, Buzdar AU, LoRusso PM, et al: A multicenter phase III trial of Xeloda (capecitabine) in paclitaxel refractory metastatic breast cancer. *Proc Am Soc Clin Oncol* 1998; 17:476A.
35. O'Shaughnessy J, Moiseyenko V, Bell D, et al. A randomized phase II study of Xeloda (capecitabine) vs CMF as first line chemotherapy of breast cancer in women aged ≥ 55 years. *Proc Am Soc Clin Oncol* 1998; 17:398A.
36. Carmichael J, Possinger K, Phillip P, et al. Advanced breast cancer: A phase II trial with gemcitabine. *J Clin Oncol* 1995; 13:2731-2736.
37. Hryniuk W and Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984; 2:1281-1288.
38. Antman KH. Dose intensive therapy in breast cancer. In: Armitage JO, Antman KH, editors. *High Dose Cancer Therapy: pharmacology, hematopoietins, stem cells*. Baltimore: Williams and Wilkins, 1992; 701-718.
39. Peters WP, Shpall EJ, Jones RB, et al. High dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. *J Clin Oncol* 1988; 6:1368-1376.
40. Williams SF, Gilewski T, Mick R, et al. High-dose consolidation therapy with autologous stem-cell rescue in stage IV breast cancer: A follow-up report. *J Clin Oncol* 1992; 10:1743-1747.
41. Antman K, Ayash L, Elias A, et al. A phase II study of high dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard dose therapy. *J Clin Oncol* 1992; 10:102-110.

42. Elias AD, Ayash L, Anderson KC, et al. Mobilization of peripheral blood progenitor cells by chemotherapy and granulocyte macrophage colony of stimulating factor for hematologic support after high-dose intensification for breast cancer. *Blood* 1992; 79:3036-3044.
43. Ayash LJ, Elias A, Wheeler C, et al. Double dose-intensive chemotherapy with autologous marrow and peripheral-blood progenitor-cell support for metastatic breast cancer: A feasibility study. *J Clin Oncol* 1994; 12:37-44.
44. Patrone F, Ballestrero A, Ferrando F, et al. Four-step high-dose sequential chemotherapy with double hematopoietic progenitor-cell rescue for metastatic breast cancer. *J Clin Oncol* 1995; 13:840-846.
45. Schpall EJ, Jones RB, Bearman SI, et al. Transplantation of enriched CD34-positive autologous marrow into breast cancer patients following high dose chemotherapy: Influence of CD34-positive peripheral-blood progenitors and growth factors on engraftment. *J Clin Oncol* 1994; 12:28-36.
46. Bearman SI, Shpall EJ, Jones RB, et al. High-dose chemotherapy with autologous hematopoietic progenitor cell support for metastatic and high-risk primary breast cancer. *Semin Oncol* 1996; 23(suppl2): 60-67.
47. Peters WP, Ross M, Vredenburgh JJ, et al. High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol* 1993; 11:1132-1143.
48. Stadtmauer EA, O'Neill A, Goldstein LJ, et al. Phase III randomized trial of high dose chemotherapy (HDC) and stem cell support (SCT) shows no difference in overall survival or severe toxicity compared to maintenance chemotherapy With cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) for women with metastatic breast cancer who are responding to conventional chemotherapy: The Philadelphia Intergroup Study (PBT-1) (abstract). *Proc Am Soc Clin Oncol* 1999; 18:1A.
49. Bezwoda,WR: Randomized, controlled trial of high dose chemotherapy (HD-CNVp) versus standard dose (CAF) chemotherapy for high risk surgically treated, primary breast cancer (abstract). *Proc Am Soc Clin Oncol* 1999; 18:4A.
50. Peters W, Rosner G, Vredenburgh J, et al. A prospective, randomized comparison of two doses of combination alkylating agents (AA) as consolidation after CAF in high risk primary breast cancer involving ten or more axillary lymph nodes (LN); Preliminary results of CALGB 9082/SW0G-9114/NCIC MA13 (abstract). *Proc Am Soc Clin Oncol* 1999; 18:2A.
51. The Scandinavian Breast Cancer Study Group: Results from a randomized adjuvant breast cancer study with high dose chemotherapy with CTC supported by autologous bone marrow stem cells versus dose escalated and tailored FEC therapy (abstract). *Proc Am Soc Clin Oncol* 1999; 18:3A.
52. Wood WC, Budman DR, Korzun AH, et al: Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. *N Engl J Med* 1994; 330:1253-1259.
53. Fisher B, Anderson S, Wickerham DL, et al. Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-22. *J Clin Oncol* 1997; 15:1858-1869.
54. Davidson NE and Kennedy MJ Dose intensive chemotherapy for breast cancer: What is the evidence? In: Harris JR, Lippman ME, editors. *Diseases of the Breast Updates*. Cedar Knolls, NJ: Lippincott Williams & Wilkins Healthcare, 1998; 2(3), 4.
55. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989; 244:707-712.
56. Akiyama T, Sudo C, Ogawara H, et al. The product of the human c-erbB-2 gene: A 185 kilodalton glycoprotein with tyrosine kinase activity. *Science* 1986; 232:1644-1646.
57. Carter P, Presta L, Gorman CM, et al. Humanization of an anti-p185HER2 antibody for human cancer therapy. *Proc Natl Acad Sci USA* 1992; 89:4285-4289.
58. Baselga J, Norton L, Albanell J, et al. Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu overexpressing human breast cancer xenografts. *Cancer Res* 1998; 58:2825-31.
59. Baselga J, Tripathy D, Mendelsohn J, et al. Phase II study of weekly intravenous recombinant humanized anti-p185 HER2 monoclonal antibody in patients with HER2/neu overexpressing metastatic breast cancer. *J Clin Oncol* 1996; 14:737-744.
60. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2 overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999; 17:2639-2648.
61. Slamon D, Leyland-Jones B, Shak S, et al. Addition of Herceptin (humanized anti-HER-2 antibody) to first line chemotherapy for HER-2 overexpressing metastatic breast cancer (HER-2+/MBE) markedly increases anti-cancer activity: A randomized multinational controlled phase III trial (abstract). *Proc Am Soc Clin Oncol* 1998; 17:377A.
62. Fornier M, Seidman, AD, Esteva FJ, et al. Weekly herceptin + one hour taxol: Phase II study in HER-2 over expressing and non-over expressing metastatic breast cancer (abstract). *Proc Am Soc Clin Oncol* 1999; 18:482A.
63. Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; 90:1371-1388.
64. Cummings SR, Eckert S, Krueger KA et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA* 1999; 281: 2189-2197.

65. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989; 81:1879-1886.
66. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomized controlled trial. *Lancet* 1999; 353:1993-2000.
67. Dombrowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998; 16:453-461.
68. Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: Results of overview analysis of two phase III trials. Arimidex Study Group. *J Clin Oncol* 1996; 14:2000-2011.
69. Scheid V, Buzdar AU, Smith TL, et al. Clinical course of breast cancer patients with osseous metastasis treated with combination chemotherapy. *Cancer* 1986; 58:2589-2593.
70. Paterson AH, Powles TJ, Kanis JA, et al. Double-blind controlled trial of oral clodronate in patients with bone metastasis from breast cancer. *J Clin Oncol* 1993; 11:59-65.
71. van Holten-Verzantvoort AT, Kroon HM, Bijvoet OL, et al. Palliative pamidronate treatment in patients with bone metastases from breast cancer. *J Clin Oncol* 1993; 11:491-498.
72. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol* 1998; 16:2038-2044.



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