Update on the Management of Advanced Breast Cancer

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ABSTRACT

Recent trials comparing single-agent vs combination therapy in metastatic breast cancer suggest that it may be time to reconsider the belief that combination chemotherapy is the gold standard of treatment. Based on the limited randomized trial data available to date, high-dose chemotherapy with stem-cell rescue should not be viewed as "state-of-the art" treatment for metastatic disease and should be used only in the context of clinical trials. Recent trials have explored the optimal dosing and scheduling of the taxanes, as well as the possible role of these agents in combination regimens. Capecitabine (Xeloda), a new oral fluoropyrimidine, appears to be comparable in efficacy to CMF (cyclophosphamide, methotrexate, and fluorouracil), and preclinical data suggest possible synergy between this agent and the taxanes. Other promising agents under study include liposome-encapsulated doxorubicin (TLC D-99), an immunoconjugate linking a chimeric human/mouse monoclonal antibody to doxorubicin molecules; MTA (LY231514), a multitargeted antifolate; and marimistat, a broad-spectrum matrix metalloproteinase inhibitor. Tamoxifen (Nolvadex) remains the most important hormonal agent, but new antiestrogens and selective estrogen receptor modulators (SERMs) may provide alternatives. The potential role of new aromatase inhibitors as first-line hormonal agents requires further study. Finally, the possible synergy between trastuzumab (Herceptin), a recombinant humanized monoclonal antibody to the HER-2/neu protein, and paclitaxel (Taxol) is being studied in two clinical trials.

Breast cancer is the most frequently diagnosed cancer in American women, and the second most common cause of cancer death.[1] Over the past several decades, there has been a fairly steady increase in the incidence of the disease. Epidemiologic data from the United States analyzed between 1988 and 1990 indicate that the lifetime risk of developing breast cancer is 12.2%, or, stated in another way, one in eight women will develop the disease at some point during her life.[2]

Although approximately 80% of breast cancer patients present with disease limited to the breast and/or axillary lymph nodes, almost half of these patients later develop metastatic disease and eventually succumb to it. Metastatic breast cancer represents a historically incurable condition despite the judicious use of various hormonal manipulations, as well as surgical and radiotherapeutic interventions, and the application of active cytotoxic chemotherapeutic agents for hormone-refractory disease. For most patients with metastatic disease, treatment provides only temporary control of cancer growth. Outside of experimental protocols, the goals of management, therefore, are to palliate symptoms with as little treatment-related toxicity as possible and to extend the duration of high-quality life.

Metastatic breast cancer is moderately sensitive to chemotherapy, with 25% to 40% of patients achieving a partial or, less commonly, complete response to single-agent therapy; the duration of such responses averages 6 months.[3] Historically, the most commonly used cytotoxic agents in the management of metastatic breast cancer have been cyclophosphamide (Cytoxan, Neosar), methotrexate, fluorouracil, doxorubicin, and, more recently, the taxanes. When the disease progresses further, vinorelbine (Navelbine) and other vinca alkaloids, mitomycin (Mutamycin), mitoxantrone (Novantrone), gemcitabine (Gemzar), etoposide, and cisplatin (Platinol) represent some of the other frequently used cytotoxic drugs.

Combination vs Single-Agent Chemotherapy

Combinations of two, three, or more chemotherapeutic agents are occasionally employed based on preclinical data suggesting improved antitumor activity (ie, additive or synergistic effects); many of these combinations are derived empirically, however. Although combination regimens may sometimes yield higher response proportions than single-agent therapy, this can occur at the cost of greater toxicity, perhaps resulting in an overall lower therapeutic index.[4] This issue was specifically addressed by two studies presented at the 34th annual meeting of the American Society of Clinical Oncology (ASCO) in 1998.

The first study, conducted by the Finnish Breast Cancer Group, randomized 303 breast cancer patients with distant metastases to one of two regimens: (1) single-agent chemotherapy with epirubicin (20 mg/m² weekly until disease progression or a cumulative dose of 1,000 mg/m²), followed by mitomycin (8 mg/m² every 4 weeks) as second-line therapy; or (2) the CEF polychemotherapy regimen, consisting of cyclophosphamide (500 mg/m²), epirubicin (60 mg/m²), and fluorouracil (500 mg/m²) every 3 weeks, followed by mitomycin (8 mg/m²) and vinblastine (6 mg/m²) every 4 weeks. Although responses to CEF tended to last modestly longer than responses to epirubicin alone (median duration, 12 vs 10.5 months; $P = .07$), no significant difference in time to progression ($P = .28$) or overall survival ($P = .65$) was found between the two arms.

Moreover, no difference in survival was seen when only the patients who received both the first- and second-line treatments were compared ($P = .96$), or when survival was calculated from the beginning of second-line therapy ($P = .56$). Single-agent therapy was also associated with less toxicity and better quality of life.[5]

The second report, presented by the International Taxotere 304 Study Group, described the results of a phase III study comparing single-agent docetaxel (Taxotere) therapy vs the combination of mitomycin and vinblastine in patients with metastatic breast cancer whose disease had progressed following an anthracycline-containing regimen. In this experience, single-agent docetaxel therapy proved more

tive than mitomycin plus vinbl
not only with respect to respons
and time to treatment failure, but
gratifyingly, with regard to sur
Median survival duration was
months in the docetaxel group
months in the mitomycin-vinbl
group ($P = .0097$).[6]

In this context, the experien
Sledge and colleagues, reported
1997 ASCO meeting, should be
sidered.[7] In that study, Eastern
erative Oncology Group Study (E
1193, single-agent therapy with
doxorubicin or paclitaxel (Taxol
compared with the combination o
orubicin and paclitaxel as firs
therapy in 739 patients with meta
breast cancer. Patients receiving si
agent therapy were crossed over
other agent at the time of disease
gression.

Monotherapy with either doxo
cin or paclitaxel had equivalent
peutic activity; the combination
two drugs resulted in superior o
response rate and time to treatmen
ure. Despite this, combination th
was not superior to sequential si
agent therapy with regard to overal
vival and quality of life.

Taken together, these trials sh
prompt a reconsideration of the
ventional wisdom that combin
chemotherapy is the "gold stand
for the treatment of metastatic b
cancer.

Is More Better?

Ultimately, the treatment of stag
breast cancer often represents an att
to reach an equilibrium between the
liation conferred by response to t
py, on the one hand, and t
ment-related toxicity, on the o
Thus, the issue of the value of
intensification is of utmost importa
since increased doses are commonl
sociated with greater toxicity.

Dose-Intensified Regimens

A trial of the Italian group Gr
Oncologico Nord-Ouest (GONO)
ported at ASCO 1998 by Lionetto
is instructive in this regard. This
randomized patients to receive e
standard doses of CEF or the same
imen in an intensified manner
growth factor support; patients in

Table 1

Randomized Trials of High-Dose Chemotherapy/Autologous Stem-Cell Rescue (HDC/ASCR) for Metastatic Breast Cancer

Trial Number/ Sponsor(s)	HDC/ASCR Arm	Control Arm	Sample Size Accrual*	Target Completion Date
PBT-01 (Philadelphia Group, ECOG, SWOG, NCCTG)	CMF/CAF × 4-6→ HDC/ASCR: CTCb	CMF/CAF × 4-6 → CMF × 2 yr	587 (standard dose) 515 (high dose)	Winter 1997
Duke University	AFM × 2-4 → HDC/ASCR: CBP	AFM × 2-4→ At relapse: CEF	80	
PEGASE	CEF× 4 → HDC/ASCR: CT	CEF × 4	180	
NCIC	A or Tx × 4 → HDC/ASCR: CMtCb × 2	Continue A (to dose limit) or Tx (9 cycles)	192	

Adapted from Zujewski J. *J Natl Cancer Inst* 90(3):200-209, 1998.

A = Adriamycin; AFM = Adriamycin, fluorouracil, methotrexate; CAF = Cyclophosphamide, Adriamycin, fluorouracil; CBP = Cyclophosphamide, BCNU (carmustine), cisplatin; CEF = Cyclophosphamide, epirubicin, fluorouracil; CMF = Cyclophosphamide, methotrexate, fluorouracil; CMtCb = Cyclophosphamide, mitoxantrone, carboplatin; CT = Cyclophosphamide, thiotepa; CTCb = Cyclophosphamide, thiotepa, carboplatin; ECOG = Eastern Cooperative Oncology Group; NCCTG = North Central Cancer Treatment Group; NCIC = National Cancer Institute of Canada; PBT = Philadelphia Transplant Group; PEGASE = Societe Francaise De Greffe Du Moelle; Federation National Du Lutte Contre Le Cancer; SWOG = Southwest Oncology Group; Tx = Taxol

* As of June 1, 1997

On the basis of the limited data available to date from randomized, prospective trials, high-dose chemotherapy cannot yet be considered "state-of-the-art" treatment for advanced breast cancer and should be offered only to patients in the setting of clinical trials. The final results of such large prospective trials are eagerly awaited (Table 1).

If multiagent chemotherapy and dose escalation prove to be suboptimal in conferring a consistent survival advantage in metastatic breast cancer, other strategies must be pursued. These include the development of newer active drugs, or the exploration of different alternatives, for example, biological therapies.

Taxanes and Beyond

The taxanes, ie, paclitaxel and docetaxel, are a relatively new addition to the chemotherapeutic arsenal against breast cancer. Their mechanism of action involves the formation of polymerized microtubules and their stabilization against the forces that lead to depolymerization. Proapoptotic effects, as well as antiangiogenic actions, may also be clinically relevant.[14,15]

The determination of optimal dosing and scheduling of taxanes has been an important objective during their development. While the clinical development of docetaxel has largely involved a single administration schedule (1-hour infusion) and a narrow dose range (60 to 100 mg/m²), the range of paclitaxel doses and schedules has been broader (varying from 80 to 250 mg/m² infused over 1 hour weekly to 3-, 24-, or even 96-hour infusions every 3 weeks).

Table 2

Randomized Trials of Single-Agent Taxanes in Metastatic Breast Cancer: Dose and Administration Schedule

Study	Dose (mg/m²)	Administration Schedule (h)	Response Rate (%)	*P* Value
Paclitaxel				
BMS 048	175 mg/m² 135 mg/m²	3 h	29% 22%	.108
BMS 071	175+ mg/m²	3 h 24 h	29% 32%	NS
NSABP B-26	250 mg/m²	3 h 24 h	40% 50%	.02
CALGB 9342	175 mg/m² 210 mg/m² 250 mg/m²	3 h	21% 28% 22%	.64
MDACC	140 mg/m² 250 mg/m²	96 h 3 h	29% 23%	NS
Docetaxel				
RPR	100 mg/m² 75 mg/m²	1 h	NA	NA

BMS = Bristol-Myers Squibb; CALGB = Cancer and Leukemia Group B; MDACC = M. D. Anderson Cancer Center; NA = Not applicable; NS = Not significant; NSABP = National Adjuvant Surgical Breast and Bowel Project; RPR = Rhône-Poulenc Rorer

Paclitaxel

• **Optimal Dose and Schedule**—Preclinical data have suggested that the duration of paclitaxel exposure may be more important than dose for the cytotoxic activity of this drug. Depending on the duration of exposure, cellular cytotoxicity can be achieved at relatively low concentrations of paclitaxel, on the order of 0.01 μM.[16,17] That duration of exposure can be an important element in the clinical activity of paclitaxel has also been demonstrated by the activity of prolonged 96-hour continuous infusions in some patients with metastatic breast cancer soon after their disease progressed during shorter infusions of the drug.[18,19] However, the administration of 96-hour continuous infusions of paclitaxel imposes a certain inconvenience for both the clinic and patient.

Many clinical trials have addressed the issue of both the optimal dosing and scheduling of the taxanes (Table 2). With regard to dosing, the results of a randomized trial of paclitaxel doses of 135 vs 175 mg/m² on a 3-hour schedule in pretreated women with metastatic breast cancer revealed no major differences in response rates (22% and 29%, respectively) or median survival durations (10.5 and 11.7 months, respectively). Progression-free survival was slightly longer with the 175-mg/m² dose than with the lower dose (4.2 vs 3 months; $P = .02$), however.[20]

In the Cancer and Leukemia Group B (CALGB) trial 9342 reported at the 1998 ASCO meeting, 450 patients were randomized to receive 175-, 210-, or 250-mg/m² doses of paclitaxel on a 3-hour schedule. The three groups did not differ with respect to response rates or survival, but the higher doses were associated with greater toxicity, particularly peripheral neuropathy (26% rate of grade 3 events). These data provided little compelling evidence to support paclitaxel 3-hour infusion dosing of greater than 175 mg/m² in women with metastatic breast cancer.[21]

Another randomized clinical tr
by M. D. Anderson Cancer Cent
tected no significant difference
jective responses or survival
paclitaxel at either 140 mg/m²
96-hour infusion or 250 mg/m²
3-hour infusion—the maximally
ated doses at these schedules.[22

Two other trials have address
timal paclitaxel scheduling. Th
domized Bristol-Myers Squibb (
071 trial, in which women with
static breast cancer were treate
paclitaxel (175 mg/m²) infused o
ther 3 or 24 hours, allowing for in
tient dose escalation as tolerate
conducted largely in Europe, C
and Israel. The two groups did n
fer significantly with respect to res
rates (29% and 32%, respectively

Similar results were obtained b
tional Surgical Adjuvant Breas
Bowel Project (NSABP) trial B-
this trial, response rates for pac
(250 mg/m²) infused over either 3
hours were 40% and 50%, respect
suggesting that the more myelosu
sive 24-hour schedule does not re
a significant improvement in ou
in the palliative setting.[24] The
sion of patients with stage IIIB d
partly explains the higher respons
portions in the NSABP B-26
as compared to the aforement
studies.

• **Weekly Administration**—A
method to provide extended cu
tive drug exposure is frequent
tive drug administration, such as
weekly schedule. Weekly dosi
paclitaxel via a 1-hour infusion has
demonstrated to be a well-tolerate
sible administration schedule
Weekly administration of paclita
both dose-intense and dose-dens
also has a favorable toxicity profi
a remarkable degree of activity
tients with metastatic breast canc

In our experience at Memorial S
Kettering Cancer Center, the over
sponse rate to a weekly administ
schedule was 53% (95% confiden
terval [CI], 34% to 72%), which
pares favorably with the activity
for 3-, 24-, and 96-hour regime
contrast to these other regimens
ever, myelosuppression was insi
cant with weekly paclitaxel, no f
neutropenia was encountered, a

tients treated with the combination regimen had a 66% incidence of grade 3-4 neutropenia, vs a rate of 32% with paclitaxel alone, and two cases of congestive heart failure occurred with the combination, vs one case with paclitaxel alone. Analysis of survival awaits longer follow-up, but these data are certainly provocative, if not surprising in light of the ECOG 1193 results with paclitaxel plus doxorubicin.[7]

Docetaxel

Regarding docetaxel, Loeffler et al reported their experience with weekly infusions in stage IV breast cancer patients.[29] Doses were escalated in increments of 5 mg/m² from 30 to 45 mg/m² weekly × 6 with a 2-week break. The overall response rate was 50%, with 15% complete remissions and 35% partial remissions; 38% of patients had stable disease. Moreover, three out of five patients with a history of prior paclitaxel therapy responded to docetaxel. These investigators observed that weekly docetaxel has activity in chemotherapy-pretreated breast cancer that is comparable to 100 mg/m² of docetaxel every 3 weeks, but with apparently less grade 3-4 leukopenia.

Another ASCO presentation by Sjöström et al focused on a phase III trial that compared docetaxel (100 mg/m²) every 3 weeks to methotrexate (200 mg/m²) plus fluorouracil (600 mg/m² on days 1 and 8) every 3 weeks (MF regimen) in 199 patients with anthracycline-resistant breast cancer.[30] The overall response rate (partial and complete) was 42% in the docetaxel arm and 19% in the MF arm ($P < .001$); median time to progression was 6 months in the docetaxel group and 3 months in the MF group ($P = .006$). These results thus demonstrated the superiority of single-agent docetaxel over MF for patients with anthracycline-resistant metastatic breast cancer.

Newer Agents

Capecitabine

Considering newer drugs for advanced breast cancer, one of the most interesting agents is capecitabine (Xeloda). Capecitabine is a novel, oral, selectively tumor-activated fluoropyrimidine carbamate that has shown promising activity in breast and colon cancers during phase I and II evaluations. This agent is sequentially converted to fluorouracil by three enzymes located in the liver and within tumors, with the final conversion step to fluorouracil catalyzed by thymidine phosphorylase, which is found preferentially in breast cancer cells as compared to surrounding normal host tissues (Figure 1).

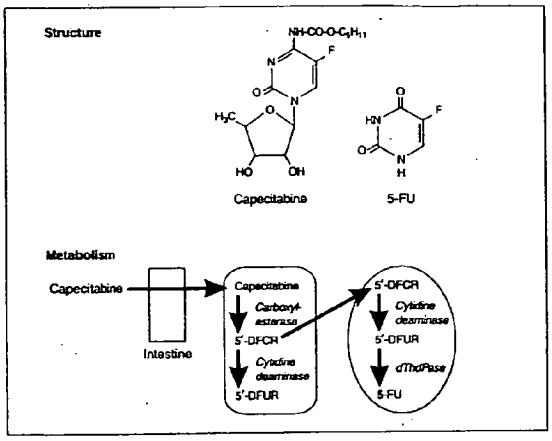

Figure 1: Chemical Structure and Mechanism of Action of Capecitabine— 5'-DFCR = 5'-Deoxy-5-fluorocytidine; 5'-DFUR = 5'-Deoxy-5-fluorouridine; dThdPase = Thymidine phosphorylase; 5-FU = Fluorouracil

An abstract presented by Blum et al at the 1998 ASCO meeting described a phase II trial of twice-daily oral capecitabine (2,510 mg/m²/d) given for 2 weeks, followed by a 1-week rest period, and repeated in 3-week cycles, among patients with paclitaxel-refractory metastatic breast cancer.[31] A total of 163 patients were enrolled by 24 centers; patients had received at least two but no more than three prior chemotherapeutic regimens, one of which contained paclitaxel as treatment for metastatic disease.

The primary study end point was tumor response in patients with measurable disease. The response rate was 20%, median response duration was 8.1 months, and median survival was 12.8 months. Moreover, in patients with baseline pain > 20 mm on a visual analog scale, 47% showed a significant improvement in pain. Diarrhea (14%) and hand-foot syndrome (10%) were the only treatment-related adverse events that occurred with a grade 3 or 4 intensity in ≥ 10% of patients. Alopecia did not occur and myelosuppression was minimal; there was no treatment-related mortality.

Given these data and the historical context of the use of continuous intravenous infusions of fluorouracil as a salvage therapy for metastatic breast cancer, capecitabine was approved by the FDA for use in patients with paclitaxel-refractory metastatic breast cancer in the spring of 1998. In summary, capecitabine can be considered an active drug in the treatment of paclitaxel-refractory advanced breast cancer with a relatively favorable toxicity profile.

- **Capecitabine vs Other Agents**—A second abstract reported at ASCO 1998 presented the results of a randomized phase II trial of capecitabine vs cyclophosphamide, methotrexate, and fluorouracil (CMF) as first-line chemotherapy for advanced breast cancer in women > 55 years old (median age in both groups, 69 years).[32] Capecitabine was given orally at a dosage of 2,510 mg/m²/d for 2 weeks, followed by 1 week of rest, and CMF was administered intravenously on day 1 every 21 to 28 days.

A total of 95 women were randomized. Response rates were 25% in the capecitabine-treated patients and 16% in the CMF recipients, and time to progression was 132 days with capecitabine vs 94 days with CMF.

Regarding toxicity, grade 3-4 clinical adverse events were reported by 44% of patients receiving capecitabine and 20% patients treated with CMF. The difference between the two groups was due primarily to hand-foot syndrome (16% vs 0%) and diarrhea (8% vs 3%). On the other hand, grade 3-4 hematologic toxicity occurred more frequently with CMF (47%) than with capecitabine (20%).

Overall, within the constraints imposed by relatively small sample sizes, it appears that home-based monotherapy with capecitabine appears to have at least comparable efficacy to CMF combination therapy in this older patient population.

Finally, in a multicenter trial presented by O'Reilly et al, the activity of capecitabine was compared to that of paclitaxel in patients with advanced breast cancer whose disease had progressed following prior anthracycline therapy.[33] In this study, two schedules of capecitabine were planned: (1) 2,510 mg/m²/d for 14 days, followed by 1 week of rest; or (2) a continuous daily schedule of 1,331 mg/m²/d. (The continuous arm of capecitabine was discontinued, however, after two patients were enrolled.[personal communication, Dr. Fabio Benedetti, Roche, Inc., February 1999]) Paclitaxel was administered at a dosage of 175 mg/m² on day 1 of each 3-week cycle.

With 41 evaluable patients, the intermittent schedule of capecitabine yielded a 36% response rate, as compared with a 21% rate with paclitaxel. Median time to progression was 92 days on the intermittent capecitabine schedule and 95 days on paclitaxel. Grade 3-4 events were reported in 22% of patients treated with capecitabine and 58% given paclitaxel.

- **Capecitabine in Combination Regimens**—In a relevant preclinical Japanese study, the efficacy of capecitabine and fluorouracil in combination with other cytostatic agents, including taxanes, was evaluated in five xenograft models of human bre cinoma cells.[34] While the co tion of fluorouracil and t demonstrated only additive e treatment with capecitabine and anes showed synergy and produ mor regression in some xe models. In fact, the taxanes in the tumor levels of thymidine ph rylase by four- to eightfold wit 10 days following the single a tration; the treatment did not i the mouse enzyme levels in nor sues (intestine and liver), howeve tumoral thymidine phosphoryla els correlate with in vivo suscep to capecitabine, it is possible t taxanes may enhance the effic capecitabine by upregulating t zyme in human cancer cells.

Reinventing Old Drugs

The continued search for agents for control of disease and tion of symptoms in metastatic cancer has also led to the manip of the more conventional drugs s achieve equivalent or possibly activity with decreased toxicity.

Liposomal Doxorubicin

One promising agent in this is liposome-encapsulated doxor (TLC D-99). A phase III trial re at ASCO 1998 evaluated its use ventional doxorubicin, both at a 75 mg/m² every 3 weeks.[35] Th randomized 69 patients who were ified on the basis of prior expos doxorubicin. During the trial, p underwent serial ventriculograp cumulative doses of 300, 400, a mg/m² and then every cycle ther Patients were removed from the if left-ventricular ejection fr (LVEF) declined by ≥ 20% fro baseline value (if this value was ≥ or by ≥ 10% from baseline (if < or if congestive heart failure deve

Response rates were 33% TLC D-99 arm and 29% in the d bicin arm. Congestive heart failu veloped in three patients (4%) with doxorubicin but in none of given TLC D-99. Also, TLC generally produced less emesis, titis, fever, and infection, sugg that it may as effective as free d bicin but perhaps safer.

reaction in 4%, and a grade 4 reaction in 15%. The skin rash problem was ameliorated with prophylactic dexamethasone.

Marimistat

Other agents under study include marimistat, a broad-spectrum matrix metalloproteinase inhibitor. This drug has already shown activity in numerous solid tumor models, including breast cancer, in which high levels of matrix metalloproteinases (enzymes instrumental in the growth and spread of malignant cells) are expressed. As reported at the 1998 ASCO meeting, an ongoing phase I study demonstrated the feasibility of using marimistat in conjunction with doxorubicin and cyclophosphamide in patients with metastatic breast cancer.[38]

Hormonal Strategies

Endocrine therapy has been a critical component of the treatment of advanced breast cancer for over a century, since Beatson published his observation of tumor response in women with metastatic breast cancer undergoing oophorectomy.[39] As hormonal interactions and their molecular mechanisms have become more well understood, more specific agents for hormonal therapy have been developed.

Over the last 2 decades, many new hormonal anticancer agents have been developed and introduced into clinical trials. However, despite this intense research, tamoxifen (Nolvadex) still remains the most important hormonal antitumor agent for breast cancer.

Tamoxifen

Tamoxifen is a synthetic antiestrogen that blocks estrogen binding to the estrogen receptor (ER). Although (unsuccessfully) designed as a contraceptive, tamoxifen's activity in metastatic breast cancer was recognized over 2 decades ago. Since then, many trials have confirmed the role of tamoxifen as a safe, effective antitumor agent. With an overall response rate of about 30% to 35% in unselected patients and a significantly higher response rate (60% to 75%) in patients with ER positive and progesterone receptor (PR) positive tumors, tamoxifen is as efficacious as many chemotherapy regimens.

A recent report of long-term follow-up from earlier studies showed a median survival of 27.2 months and a median time to progression of 6.7 months when tamoxifen was used as initial hormonal therapy in women with ER/PR positive or unknown tumors.[40] However, less than 10% activity was noted among women with ER/PR negative tumors.

Several randomized studies demonstrated that tamoxifen doses higher then 20 mg/d do not confer further advantages.[41-43] The main side effects of tamoxifen include hot flashes, thromboembolic events (3.2% in women with metastatic cancer),[44] depression, a slight increase in endometrial cancer, and reported cases of corneal and retinal disease.

- **Use in Premenopausal Women**—Although the benefits of tamoxifen in postmenopausal women are unequivocal, its use in premenopausal women has been more controversial. First, a greater proportion of premenopausal metastatic breast cancer is ER/PR negative. Second, other methods, such as surgical- or radiation-induced ovarian ablation or hormonal blockade by luteinizing hormone–releasing hormone (LHRH) agonists have been favored by some experts. In addition, some authors have long recommended a combination of tamoxifen and either medical or surgical ovarian ablation.[45]

Tamoxifen and ovarian ablation have been compared in at least three randomized, albeit small, trials, and appear to be equally effective.[46-48] A meta-analysis including four trials comparing tamoxifen and ovarian ablation (by surgery or irradiation) in premenopausal women with ER positive tumors could not identify a superior regimen. Of note, however, were the observations that an initial response to either tamoxifen or ovarian ablation was predictive of a subsequent response to the other treatment,[49] and that failure to respond to tamoxifen did not preclude further response to oophorectomy in some women.[46]

A small Italian study compared surgical ovarian ablation to medical ovarian ablation (goserelin [Zoladex]), with or without tamoxifen, in a 2 × 2 design. This study found no clear survival advantage in any of the four groups, hence suggesting that combining tamoxifen with ovarian ablation does not add any advantages. However, the patients who received concomitant tamoxifen and goserelin experienced more toxicity.[50]

- **Tamoxifen Resistance**—Unfortunately, breast cancer in most patients will eventually become resistant to tamoxifen. Tamoxifen resistance is not fully understood. None of the proposed mechanisms, such as the emergence of tamoxifen-dependent cell lines and loss or mutations of the ER, its functions, and interactions, appear to comprehensively explain resistance to tamoxifen.[51,52]

Other Antiestrogens

The significant activity and relatively modest toxicity of tamoxifen (ie, high therapeutic index) when compared with cytotoxic chemotherapy has led to an intensive search for other hormonal agents.

- **Toremifene (Fareston)**, an antiestrogen with properties similar to those of tamoxifen, was recently approved in the United States for the treatment of metastatic breast cancer. Large American and European randomized studies found no significant differences in the efficacy and safety of toremifene and tamoxifen when the two therapies were compared in postmenopausal women with ER positive or unknown tumors.[53-57] The reported response rates were between 29% to 50%. Toremifene doses higher than 60 mg/d did not offer any advantages over lower doses. A crossover trial demonstrated cross-resistance of the two drugs.[57]

- **Other novel antiestrogens** currently undergoing preclinical and clinical evaluation are droloxifene and the pure antiestrogen ICI 182780 (Faslodex). Droloxifene has been evaluated in phase II clinical trials.[58,59] Early clinical trials suggest that ICI 182780 has no adverse effects on the uterus, vagina, or brain, and that the drug is otherwise well tolerated.[60] More studies are needed to evaluate its efficacy.

- **Selective Estrogen Receptor Modulators**—The development of newer selective estrogen receptor modulators (SERMs) offers reason for optimism. Designed to be more selective and less toxic than older agents, the SERMs have shown very exciting preclinical and clinical results. One SERM, raloxifene (Evista), approved for the treatment of osteoporosis in postmenopausal women, has also dramatically reduced the incidence of new breast cancers.[61] with relatively short follow-up. A "third-generation" SERM (LY353381) has entered phase II trials for the treatment of metastatic cancer after a phase I trial showed activity in women whose disease had progressed during tamoxifen therapy.

Aromatase Inhibitors

Aromatase inhibitors block the peripheral conversion of androstendione to estrone. This effect is not specific to the ovaries, but rather, occurs in multiple organs, such as adipose tissue, muscle, and liver—the latter being important sites of estrogen production in postmenopausal women.

- **Aminoglutethimide**—The best known representative of this group is aminoglutethimide (Cytadren). When studied in women whose disease progressed while they were receiving tamoxifen, the patients with ER positive tumors had a response rate of 57%, as compared with a rate of 12% in those with ER negative tumors.[62] However, the relative lack of specificity of this agent, as well as bothersome side effects, such as adrenal suppression, skin rash, somnolence, dizziness, and gastrointestinal upset, have allowed newer more selective, less toxic aromatase inhibitors to take its place. Most of these agents are 100 to 1,000 more potent than aminoglutethimide. However, an evaluation of their efficacy as first-, second-, or third-line therapy in metastatic breast cancer awaits the completion or maturation of many ongoing studies (Table 3).

- **Anastrozole and Letrozole**—The most commonly used new aromatase agents are the triazole nonsteroidal agents anastrozole (Arimidex) and letrozole (Femara). These agents achieve a major reduction in estrogen levels without suppressing adrenal function. Within hours of administration, estradiol levels are significantly suppressed.

Anastrozole was compared with megestrol acetate (160 mg) as second-line therapy in advanced breast cancer in a three-arm randomized trial conducted in Europe. Anastrozole was administered at doses of either 1 o
mg. Responses were seen in 34% o
patients in the 1-mg group, 33.9%
the 10-mg group, and 32.8% in
megestrol acetate–group.[63]

These findings were confirme
an American study showing an ob
tive response in 27% of women tre
with 1 mg of anastrozole, 24% of t
given 10 mg of the drug, and
of those who received megestrol
tate.[64,65] Although not significa
more active, anastrozole was better
erated, with fewer cases of mild
trointestinal disturbances. Also
once-daily dosing appears to be
convenient than the four daily dos
megestrol. No difference was found
tween the two doses of anastrozole

A randomized, double-blind
compared two doses of letrozole
and 2.5 mg) with megestrol acetate
mg) as second-line therapy in 551
tients with locally advanced or m
static breast cancer. Although
significant difference in time to
gression between the 2.5-mg dos
letrozole and megestrol acetate
found, letrozole caused fewer adv
effects and was associated with b
compliance.[66] The higher (2.5-
dose of letrozole yielded significa
better overall survival than the lo
dose (0.5 mg).

- **Other nonsteroidal aroma
inhibitors** for the treatment of adva
breast cancer include fadrozole
vorozole. Fadrozole was compared
tamoxifen as first-line therapy in
rope.[67] A large, randomized trial c
pared fadrozole and megestrol ac
as second-line therapy in the Un
States.[68] Neither trial showed a
nificant difference in efficacy, bu
sults suggested that fadrozole ma
better tolerated than megestrol ace
Fadrozole and tamoxifen do not ap
to be mutually cross-resistant. In a
comparing vorozole and megestrol
tate, vorozole was better tolerated
not more efficacious.[69]

- **Steroidal Aromatase Inhibito
The steroidal aromatase inhibitors f
estane and exemestane are pres
ly being evaluated in clinical t
(Table 4). Formestane has been c
pared with tamoxifen but showed
significant difference in efficacy.[7

Table 3

Selected Trials of Endocrine Therapy in Advanced Breast Cancer

Study	Study Design	Number of Patients	Response Rate (%)	Median Duration of Response	P Value
Smith et al[84]	AG vs tamoxifen	117	30% vs 30%	15 mo vs 15+ mo	NS
Ingle et al[85]	DES vs tamoxifen	143	41% vs 33%	4.7 mo vs 5.9 mo	NS
Muss et al[86]	MPA vs tamoxifen	182	17% vs 43%	6.3 mo vs 5.5 mo	NS
Muss et al[87]	MA vs tamoxifen	138	28% vs 31%		NS
Perez Carrion et al[88]	Formestane vs tamoxifen	409	33% vs 37%	15 mo vs 20 mo	NS
Thurlimann et al[67]	Fadrozole vs tamoxifen	212	20% vs 27%	6.1 mo vs 8.5 mo	NS
Dombernowsky et al[66]	Letrozole (2.5 mg) Letrozole (0.5 mg) MA (160 mg)	551	24% 16% 13%		NS
Budzar et al[64, 65]	Anastrozole (1 mg) Anastrozole (10 mg) MA (160 mg)	764	27% 24% 30%[64]	56.1%[64]* 54.6%* 46.3%[65]*	NS
Buchanan et al[47]	OvAbl vs tamoxifen	122	24% vs 21%	7 mo vs 20 mo	NS
Pyrhonen et al[54]	Toremifene vs tamoxifen	415	31.3% vs 37.3%	7.3 mo vs 10.2 mo	NS
Goss et al[69]	Vorozole vs MA	452	10.5% vs 7.6%	18.2 mo vs 12.5 mo	NS

AG = Aminoglutethimide; DES = Diethylstilbestrol; MA = Megestrol acetate; MPA = Medroxyprogesterone; NS = Not significant; OvAbl = Ovarian ablation

*2-Year overall survival rate

transducer of mitotic stimuli.[73,74]

Like the epidermal growth-factor receptor, HER-2/neu receptor expression appears to reflect increased proliferative activity in tumors. Amplification of the HER-2/neu gene and/or overexpression of its messenger RNA (mRNA) and protein have been identified in many human cancers and are seen in 25% to 30% of breast cancers,[75] suggesting that these abnormalities may contribute to malignant transformation and tumorigenesis.[76] In fact, HER-2 overexpression has been correlated with poor outcome in patients with breast cancer.[77,78]

Trastuzumab

A recombinant humanized monoclonal antibody that binds specifically to the extracellular domain of $p185^{HER2}$, (rhuMab HER2) trastuzumab (Herceptin) has demonstrated antitumor activity against HER-2/neu-overexpressing metastatic breast cancer in phase II and III trials.[79-81] Its activity may be explained by at least three mechanisms of action: The antibody may (1) antagonize the function of the growth-signaling properties of the HER-2 system; (2) signal immune cells to attack and kill tumor cells; and (3) increase chemotherapy-induced cytotoxicity.

• **Single-Agent Trastuzumab**—Our experience at Memorial Sloan-Kettering Cancer Center with trastuzumab was reported in 1996. We treated 46 metastatic breast cancer patients whose tumors overexpressed HER-2 (as demonstrated by immunohistochemical analysis using the murine monoclonal antibody 4D5) with trastuzumab at an initial loading dose of 250 mg and subsequent weekly doses of 100 mg. These patients had received a median of three prior chemotherapy regimens.

All toxicities were minimal, and no human antihuman antibodies (HAHA) against trastuzumab were detected in any patient. An overall response rate of 11.6% was observed, including one complete and four partial remissions. As of this writing, one patient remains in complete remission after > 2.5 years of trastuzumab therapy.

This observation was expanded and confirmed in a multinational trial reported at ASCO 1998 by Cobleigh et al, which evaluated the efficacy and safety of trastuzumab given as a single agent in 222 women with HER-2–overexpressing metastatic breast cancer.[80] Trastuzumab was delivered at an initial loading dose of 4 mg/kg and subsequently at a weekly dose of 2 mg/kg. All patients had been pretreated with chemotherapy: 69% had received adjuvant therapy, 32% had had one regimen for metastatic disease, 68% had had two regimens, and 25% had received prior high-dose chemotherapy.

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Table 4

Ongoing Trials of Endocrine Therapy in Metastatic Breast C

Study	Trial Type	Design
RPCI-DS-97-29, NCI-G98-1412	Phase III, double-blind, randomized	ICI 182780 vs anas postmenopausal wo advanced breast ca
Novartis 2026701025, NCI-V98-1388,	Phase III, double-blind, randomized	Letrozole vs tamoxif postmenopausal wo with stage IIIB, meta or recurrent breast c
SB-223030/010	Phase III, randomized	Idoxifene vs tamoxif postmenopausal wo with metastatic breas cancer
SWOG-9630	Phase III, randomized	Medroxyprogesteron patients with breast c
MSKCC-98038, NCI-G98-1451	Phase II, double-blind, randomized	SERM III* LY353381 20 mg vs
SVMC-V89-0296, NCI-V89-0296	Phase I/II	High-dose megestrol women with metastat breast cancer, endo cancer, or mesotheli
EORTC-10951	Phase II	Exemestane vs tamo women with locally re or metastatic breast c
NCI-96-C-0080B, NCI-T95-0090N, NYU-9440	Phase I	9-*cis*-retinoic acid and tamoxifen in women w advanced breast canc

EORTC = European Organization for Research and Treatment of Cancer; MSKCC = Memorial Sloan-Kettering Cancer Center; NCI = National Cancer Institute; NYU = New York University; RPCI-DS = Roswell Park Cancer Institute; SB = SmithKline Beech SVMC = Saint Vincent Medical Center; SWOG = Southwest Oncology Group; SERM = Selective estrogen receptor modulator

*Trial of two dose levels in women with locally advanced metastatic breast cancer

After a median follow-up of 11 months, the investigator-determined overall response rate was 21% (95% CI, 16% to 27%), with a 4% rate of complete remissions. The independent response evaluation committee–determined response rate was 15% (95% CI, 10% to 20%). The median response duration was 8.4 months. Reduction in cardiac ejection fraction was observed in nine patients, of whom six were symptomatic; all either had received prior anthracycline therapy or had a significant cardiac history at entry.

In summary, trastuzumab has a favorable toxicity profile, is active as a single agent in women with HER-2–overexpressing metastatic breast cancer, and induces durable objective tumor responses.

• **Trastuzumab Combined Chemotherapy**—Slamon et al p ed the results of a phase III t trastuzumab in 469 patients with 2–overexpressing metastatic brea cer at the 1998 ASCO meeting.[8 trial was based on observations clinical models of synergy betwee tuzumab and some chemothera agents, in particular, doxorubici paclitaxel. For example, Baselga demonstrated marked synergistic tumor activity for paclitaxel plus body against HER-2–overexpre mammary carcinoma cells.[82]

In the phase III trial, patien ceived either doxorubicin (60 m plus cyclophosphamide (600 mg/ they had not received doxorubi the adjuvant setting, or paclitaxel

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