New Cytotoxic Agents for the Treatment of Breast Cancer

Over the past 5 years, many new cytotoxic agents with activity against metastatic cancer have been discovered, and several are currently undergoing clinical trials. Whether their marked degree of activity represents a real

Introduction

Over the past 10 years, several new treatment strategies have been developed and many new agents have been evaluated for the treatment of metastatic breast cancer [1]. Some of these agents represent analogs of previously existing drugs, whereas others belong to new molecular families. Some agents have novel mechanisms of action, different from those of drugs used in the past. Several agents have been approved by the regulatory agencies for the treatment of breast cancer; others are still completing clinical evaluation, and many more are in preclinical evaluation. In this article, I will review agents with demonstrated efficacy against breast cancer (Table 1).

Amonafide

Amonafide (benzisoquinolinedione, nafidimide) is a synthetic compound with potent antiviral and cytotoxic activity. It acts as a DNA-intercalating agent and is an inhibitor of topoisomerase II [2]. Phase I trials using 3 different schedules were conducted: daily 5 every 3 weeks, bolus infusion every 3 to 4 weeks, and 24-hour continuous infusion every 4 weeks. The dose-limiting toxicity was reversible myelosuppression. Nonhematologic toxicity was mild, consisting mostly of nausea and vomiting, which was easily controlled with antiemetics. The daily 5 schedule of administration was recommended for phase II trials. The recommended phase II dosage was 300 mg/m² daily for 5 consecutive days. The daily dose was administered over 1 hour. Amonafide has modest antitumor activity against prostate and small-cell lung cancer. Three phase II trials performed in patients with breast cancer have been reported [3-5]. The overall activity of the drug was modest, between 15% and 20%. Two complete remissions were observed among 103 patients. The response rate was modest, even in patients who had undergone no prior chemotherapy.

Amonafide is acetylated to N-acetyl-amonafide [6,7]. Because of the known, marked individual variation in plasma concentration of N-acetyl-amonafide, an acetylator phenotype was determined in a small group of patients. Fast acetylators were found to have a much higher overall response rate (3 of 8; 38%) than slow acetylators (1 of 16; 6%). An acetylator phenotype also correlated with toxicity, suggesting that the recommended phase II dose was too high for fast acetylators and too low for slow acetylators (Table 2). Additional trials are indicated for this agent to confirm this latter observation, which suggests that in a subgroup of patients with breast cancer, amonafide has marked antitumor activity. Dosing based on an acetylator phenotype is being tested prospectively to improve the therapeutic ratio of this agent. Because extramedullary toxicity is modest, additional dose-escalation studies, perhaps with hematopoietic growth factor support, would be indicated to assess the full range of doses with this agent.

New Anthracyclines

Anthracyclines are the most active single agents in the treatment of breast cancer, but their clinical usefulness is limited by cardiotoxicity related tocumulativeos[8]. Epirubicin is a potentially less cardiotoxic doxorubicin analog, but it has not been approved by the Food and Drug Administration (FDA) because of insufficient supportive evidence. Several new anthracycline derivatives have entered clinical trials, and a few of them have been evaluated against metastatic breast cancer [8].

Theprubicin underwent phase II evaluation in the 1980s; several trials suggested activity equivalent to that of doxorubicin [9,10]. Limited phase II trials of theprubicin in combination therapy
suggested no difference in activity between theplubicin- and doxorubicin-containing combinations [11]. However, no direct comparative trials have been reported.

**Liposomal Doxorubicin (TLC D-99)**--A new approach to reduce the toxicity of anticancer drugs is to encapsulate otherwise soluble drugs into multilamellar lipid particles (liposomes). Doxorubicin is the single most studied anticancer drug encapsulated in liposomes. TLC D-99 was developed with the intent of reducing the cardiotoxicity of doxorubicin. Phase I trials determined that an intermittent 3-weekly schedule was appropriate, and the maximum tolerated dose was found to be between 60 and 90 mg/m². Activity was similar to that of other anthracyclines in limited phase II studies [12]. In combination with standard agents, liposomal doxorubicin achieved efficacy similar to that of standard anthracycline-containing regimens [13]. To date, results suggest that higher cumulative doses can be administered with a lower incidence of and less severe cardiotoxicity than those of the soluble free agent. However, comparative trials to determine the relative efficacy and safety of this agent are just completing accrual. Other liposome-encapsulated anthracyclines are entering phase I/II studies, but the results of such studies have not yet been published.

**Anthrapyrazoles**

The anthracenediones (mitoxantrone [Novantrone], bisantrene, and others) were developed to reduce the frequency and severity of anthracycline-induced cardiotoxicity [14]. Although mitoxantrone is less cardiotoxic than the anthracyclines, it is also somewhat less effective. For this reason, mitoxantrone has not received FDA approval for treatment of breast cancer. The anthrapyrazoles are structurally similar to mitoxantrone [15]. They maintain the planar conformation and cationic nature of the anthracyclines, essential for DNA intercalation. Several anthrapyrazoles have been developed.

**Losoxantrone (CI-941)**--Preclinical evaluation demonstrated that losoxantrone induced both single- and double-stranded breaks in DNA and was a potent inhibitor of DNA synthesis [16]. In preclinical models, it was less cardiotoxic than doxorubicin [17]. Phase I clinical trials demonstrated that when losoxantrone was administered in an intermittent single-dose schedule, the maximum tolerated dose was 55 mg/m², and the dose-limiting toxicities were leukopenia and neutropenia [18]. At least two phase II studies of losoxantrone have been reported [19,20]; both included previously untreated and previously treated patients with metastatic breast cancer. The objective response rates obtained in these studies are shown in Table 3. A few complete remissions were observed, and response durations in these trials compared favorably with those expected after standard combination chemotherapy. Toxicity consisted mostly of leukopenia, although up to 40% of patients were reported to have alopecia. Acute toxicity was negligible. However, a recent update reported that 3% of patients developed congestive heart failure [21]. Therefore, this agent is as active as or more active than existing anthracyclines; however, the drug is not devoid of cardiotoxicity.

**Telexantrone (CI-937)**--This second anthrapyrazole has also completed phase I/II clinical trials [22,23]. At least one phase II study in breast cancer has been reported in abstract form [23]. At an early stage of follow-up, there were major objective responses in 9 of 47 patients, and a minor response was achieved in another 11% (Table 3). No additional information is available about this trial. The pattern, frequency, and severity of toxicity appeared to be similar to those of losoxantrone.

**Piroxantrone**--Piroxantrone hydrochloride (oxantrazole, NSC-349174) is the third anthrapyrazole compound currently undergoing testing in clinical trials [24]. No reports of its activity in breast cancer are available at this time.

**Camptothecin Analogs**

Topoisomerases are recognized targets for anticancer agents. Topoisomerase I makes a single cut in the DNA duplex and relieves transcription-associated torsional strain. Camptothecin, a plant alkaloid with broad-spectrum activity and a novel mechanism of action, was isolated from *Camptotheca acuminata* more than 2 decades ago. In the early 1970s, phase I clinical trials showed marked hematologic and nonhematologic toxicity, including severe cystitis; this led to the conclusion that the compound was too toxic for clinical development. More recently, several novel semisynthetic and synthetic analogs designed to be less toxic and to overcome the problems associated with pharmaceutical formulations of natural products have appeared. These analogs are completing clinical development. The parent compound and the recently developed analogs inhibit both DNA and RNA synthesis by topoisomerase I-mediated effects [25]. The analogs of interest in the area of breast cancer research and treatment include topotecan, irinotecan, and probably SN-38. The relative efficacy and toxicity of the camptothecin analogs were evaluated in preclinical models [26].
Topotecan--Topotecan is a potent, water-soluble camptothecin analog with a broad spectrum of antitumor activity, including human colorectal, non-small-cell lung, ovarian, breast, and renal cell carcinomas [25]. In phase II trials, topotecan was administered at a dosage of 1.5 mg/m² daily for 5 consecutive days to patients with metastatic breast cancer who had received minimal or no prior chemotherapy treatment. Cycles of treatment were repeated every 3 weeks [27]. Sixteen patients had been treated at the time of the report, 14 of whom were evaluable. Five patients achieved a partial response (36%), and 1 patient achieved a minor response. Three patients had stable disease, with the remaining five patients showing progression of metastatic disease. Myelosuppression, especially granulocytopenia, was observed. Mild fatigue, mild to moderate alopecia, and skin rashes were also reported.

Irinotecan (CPT-11) is another water-soluble camptothecin analog. Although it also is a topoisomerase I inhibitor, unlike camptothecin and topotecan, CPT-11 has limited antitumor activity in vitro. In vivo, it is converted to 7-ethyl-10-hydroxy-camptothecin (SN-38), a metabolite with a 100-fold greater antitumor activity than CPT-11 in vitro. This agent has antitumor activity against small-cell and non-small-cell lung cancer, gynecologic and gastrointestinal tumors, and leukemia and lymphoma. Until recently, severe side effects, such as leukopenia and diarrhea, had limited its clinical development.

In a recently reported phase II trial, irinotecan was administered to patients with metastatic breast cancer who had undergone minimal or no prior chemotherapy [28]. The agent was administered intravenously over 30 minutes at a dosage of 350 mg/m² every 3 weeks. Of 29 patients treated, 21 were evaluable at the time of the report; these patients had a good performance status and a moderate amount of tumor burden. Twelve patients were evaluable for response. One achieved a complete remission, whereas four others experienced no change. The remaining seven patients had progressive disease. Grade II or higher nausea and vomiting, diarrhea, abdominal cramps, alopecia, neutropenia, asthenia, and hot flashes were reported. Three patients were removed from the study because of toxicity.

In a second study, reported in abstract form only, 15 (23%) of 65 patients responded to irinotecan treatment [29]. No information is available about the duration of treatment or the effect of camptothecin analogs on quality of life.

Elliptinium Analogs

Elliptinium acetate is a plant alkaloid developed more than 20 years ago. Initial clinical evaluation demonstrated antitumor activity against breast, kidney, and other cancers [30,31]. Although the drug was of interest because of its activity and lack of myelosuppressive toxicity, other side effects (hemolytic anemia and renal failure) aborted its clinical development. More recently, novel semisynthetic analogs, with molecular modifications suggesting that the severe dose-limiting toxicities of the parent compound would be absent, have entered phase I clinical trials [32]. Extended evaluation of these compounds is awaited with interest.

New Antifolates

Several new antifolates have been developed over the past decade [33]. Trimetrexate and edatrexate have been evaluated extensively in patients with breast cancer. Lometrexol is at an earlier stage of development; its antitumor activity cannot yet be quantified for patients with breast cancer [34]. These agents target dihydrofolate reductase, and inhibition of this enzyme is their major mechanism of action. At this time, the most successful compound in clinical development appears to be edatrexate (10-EDAM) (Table 4). This agent has marked antitumor activity against metastatic breast cancer, with tolerable toxicity [34a-37]. However, because its toxicity is not completely predictable, additional clinical trials in which edatrexate is combined with folinic acid are ongoing. Trimetrexate has shown evidence of antitumor activity, albeit more modest than that observed with edatrexate [38,39].

Gemcitabine

Gemcitabine (Gemzar) is a water-soluble deoxycytidine analog and, therefore, a pyrimidine antimetabolite. It inhibits DNA synthesis and has a longer intracellular accumulation phase than cytarabine, a related compound. Gemcitabine has demonstrated antitumor activity in ovarian, head and neck, pancreatic, and non-small-cell lung cancer [40,41].
Phase I studies of gemcitabine have demonstrated that 1,200 mg/m²/wk for 3 of every 4 weeks is an appropriate dosage for phase II studies. A phase II evaluation of this agent following this dose and schedule of administration was completed in 44 patients with minimally treated metastatic breast cancer [42]. Nine (29%) of the evaluable patients achieved a partial response. Toxicity included neutropenia, liver function abnormalities, nausea, vomiting, lethargy, and alopecia. Overall, treatment was well tolerated, and confirmatory trials are ongoing. Based on these early results, gemcitabine-based combinations have been developed, and their evaluation in patients with breast cancer has been initiated. Gemcitabine was recently approved by the FDA for the treatment of advanced and metastatic pancreatic cancer.

**Miltefosine**

Synthetic phospholipids have antitumor activity, although their mechanism of action is not well defined [43]. They are known to inhibit protein kinase C, an essential step in the growth factor signal transduction in cellular proliferation. Miltefosine (hexadecylphosphocholine) has marked antitumor activity in vitro and in vivo. It differs from other synthetic phospholipids in its lack of a glycerol backbone. Miltefosine is used as a 6% solution in an aqueous 3-alkyloxypropylene glycol mixture. With oral administration of miltefosine in preclinical studies, hyperplastic gastrointestinal tract changes, gonadal atrophy, hair loss, and ocular toxicity were observed; however, no systemic effects have been observed after dermal application.

Phase II studies performed in patients with breast cancer metastatic to skin demonstrated substantial antitumor activity (Table 5) [44-47]. In some of these trials, miltefosine was employed simultaneously with other anticancer therapy, including chemotherapy or hormone therapy. Because of the lack of systemic effects of miltefosine, these combinations can be accomplished without added toxicity. However, because combination studies are more difficult to assess, the antitumor efficacy of miltefosine as part of a combination remains undefined. Additional clinical trials of the compound are ongoing, including phase II and phase III trials. In the United States, clinical trials of miltefosine have not yet begun.

**Vinca Alkaloids**

The vinca alkaloids vincristine (Oncovin) and vinblastine (Velban) have been available for the treatment of breast cancer for several decades. The existing data suggest that vinblastine is more effective than vincristine [48]. In fact, after first-line therapy, vincristine has no demonstrable antitumor activity (at currently used dosage schedules), whereas vinblastine retains substantial efficacy.

Vindesine (Eldesine) underwent clinical trials more than a decade ago; it was shown to have an efficacy similar to that of vinblastine [48]. However, vindesine was never approved by the FDA in the United States because available evidence did not suggest a better therapeutic ratio than that offered by vinblastine.

Approximately 10 years ago, vinorelbine (Navelbine), a norvinblastine derivative, underwent clinical trials.49 The most successful schedule of administration was a short intravenous infusion, repeated weekly. Phase II studies were initiated at 30 mg/m²/wk. In most studies, the actual dosage administered varied from 20 to 25 mg/m²/wk. Tolerance was excellent, with minimal nausea or vomiting, mild alopecia, rapidly reversible myelosuppression, and minimal neurotoxicity. The efficacy of this agent in first-line and second-line therapy for metastatic breast cancer is shown in Table 6 [50-57]. The activity of vinorelbine as a single agent in first-line therapy for metastatic breast cancer appears equivalent to that of the most effective single agents available today [58]. It retains substantial activity in second- and third-line treatment, although for anthracycline-refractory disease, it is less efficacious [ 59]. Because of its excellent tolerance, this agent has been used successfully for the management of elderly patients and of patients with significant comorbid conditions.

**Taxanes**

**Paclitaxel**—Paclitaxel (Taxol) was identified and studied in the laboratory more than 2 decades ago [60]. It is derived from the bark of the western yew (Taxus brevifolia). As a tubulin-active agent, it enhances tubulin polymerization and stabilizes microtubules. Paclitaxel has a broad spectrum of activity against solid tumors. Multiple schedules of administration were tested in phase I trials, but phase II studies were initiated mostly with a 24-hour infusion schedule, with cycles repeated every 3 weeks. Subsequently, other
schedules of administration were added, including 3-hour administration and a 96-hour administration every 3 weeks [61,62]. With demonstrated antitumor activity against non-small-cell carcinoma of the lungs, head and neck cancer, ovarian cancer, and other solid tumors, paclitaxel was also shown to have marked antitumor activity against metastatic breast cancer. Its efficacy, according to the extent of prior treatment of disease, is shown in Table 7 [61,63-70]. The agent retains considerable activity after prior chemotherapy exposure, including anthracycline-resistant tumors [62,67,69]. Paclitaxel is currently being evaluated in combination chemotherapy [71].

**Docetaxel**—A second taxane, docetaxel (Taxotere), has also been developed in recent years. It was recently approved by the FDA for anthracycline-resistant advanced or metastatic breast cancer. Structurally, docetaxel is quite similar to paclitaxel [68]. In preclinical studies, the spectrum of antitumor activity of the two taxanes is slightly different, and, in some models, docetaxel appears to be more effective than paclitaxel[72,73]. Phase I studies suggested that 100 mg/m² of docetaxel administered over 1 hour every 3 weeks was the appropriate phase II dose and schedule of administration. Phase II trials in patients with previously untreated metastatic breast cancer showed substantial antitumor activity (Table 8) [74-76]. Considerable activity is obtained, even in strictly defined anthracycline-resistant groups [77-80]. Both taxanes are currently under evaluation in combination with doxorubicin, fluorouracil, cyclophosphamide (Cytoxan, Neosar), vinorelbine, cisplatin (Platinol), edatrexate, and many other agents. The dose-limiting toxicity of both taxanes is severe, but neutropenia is rapidly reversible. Hypersensitivity reactions occur frequently with paclitaxel but can be eliminated almost completely with a three-drug premedication regimen, including dexamethasone, diphenhydramine, and cimetidine [71]. Although hypersensitivity reactions occur much less frequently with docetaxel than with paclitaxel, a current premedication regimen often used for this drug includes 3 to 5 days of corticosteroids; this is performed mostly to prevent, or decrease the incidence and severity of, skin toxicity and fluid retention. Other commonly observed side effects include myalgia, arthralgia, and peripheral neuropathy (paresthesias) with paclitaxel; onycholysis, peripheral edema, as well as the development of serosal effusions commonly occur with docetaxel.

**Conclusions**

Between the registration of doxorubicin in the mid-1970s and paclitaxel and docetaxel in the 1990s, no additional new and active drugs have been approved in the United States with metastatic breast cancer as an indication. Although cisplatin has marked antitumor activity as first-line therapy for metastatic breast cancer, this agent has never been registered for use in breast cancer. Over the past 5 years, the new cytotoxic agents described here have entered into clinical evaluation. All agents have demonstrated activity against metastatic disease, and several agents are currently undergoing phase I, phase II, and phase III evaluation in combination therapy as well as part of multimodality treatments of primary breast cancer. Whether the marked degree of activity shown for several of these agents is a real difference over that of drugs developed in the 1970s and early 1980s, or is simply a reflection of changes in methodology (including the performance of phase II and phase III studies in previously untreated patients) is difficult to ascertain. It is even more difficult to define the most appropriate setting in which to employ these agents in the management of breast cancer. Certainly, vinorelbine and paclitaxel have been integrated successfully into the second-line management of breast cancer[71,81], although, at this time, vinorelbine has not been approved by the FDA for use in metastatic breast cancer. Single-agent vinorelbine and single-agent paclitaxel have also been used for the management of patients with untreated metastatic breast cancer, especially patients who are elderly or patients who have comorbid conditions that preclude the use of anthracyclines or combination chemotherapy. However, whether combinations of these drugs are truly more effective than single agents utilized at the maximum tolerated dose needs to be determined. Furthermore, the effect of single agents, or combinations based on these agents, on response rate, response duration, survival, and quality of life must be ascertained.

It is unlikely that any of these agents alone will change the natural history of metastatic breast cancer. Therefore, the options to be explored include adding these single agents to existing combinations (cyclophosphamide, methotrexate, fluorouracil [CMF]; or fluorouracil, Adriamycin, cyclophosphamide [FAC]), substituting these agents for other agents in existing combinations, or developing entirely new combinations of agents listed in Table 1. These new combinations must then be compared with existing and commonly used combinations to determine which one(s) will become...
the treatment of choice for untreated patients with metastatic breast cancer. The availability of these many new, active, and well-tolerated cytotoxic agents provides a tremendous opportunity to review the impact of chemotherapy on metastatic breast cancer; through this process, we may learn the best way to integrate these compounds into the curative treatment of primary breast neoplasms.

References:
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