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Review paper

New developments in chemotherapy for metastatic breast cancer

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Breast cancer remains a major cause of morbidity and early death for women. Despite aggressive implementation of preventive measures including screening and adjuvant therapy, this disease will likely continue to have a significant impact unless better treatments are found. A number of new agents have recently been developed that show promising results in the setting of metastatic disease including losoxantrone, vinorelbine, edatrexate, paclitaxel and docetaxel. Some have shown exciting activity where tumor progression has occurred following anthracycline therapy. Appropriate evaluation of new chemotherapeutic agents requires a clear description of the population studied as well as standardized assessments of outcomes. Evaluations are more relevant and more quickly done in multicenter trials. Because of the heterogeneity of metastatic breast cancer and differences in outcome measurement, randomized trials continue to be essential in defining which agents are the most appropriate candidates for further study.

Key words: Breast cancer, chemotherapy, metastatic.

Introduction

Breast cancer continues to be a major cause of death as well as potential years of life lost for women in the western world.[1,2] It is also a significant cause of morbidity, interfering with a woman's role in the workplace as well as that of spouse and mother. Although inroads have been made to reduce mortality by early detection and adjuvant therapy, there is much room for improvement. Considerable efforts are needed to increase the availability of, and compliance with, mammography and breast self-examination.[3–5] Adjuvant therapy for early disease needs to be delivered to minority groups and those with a lower level of education as effectively as the rest of society.[6] Given these facts as well as the increasing proportion of elderly in the developed world where breast cancer is most prevalent, this disease will continue to be a major scourge well into the next century unless breakthroughs in prevention, diagnosis or management occur. We will not know for some time the results of breast cancer prevention studies.[7] Although effective delivery of dose intensity promises some breakthroughs, particularly in high risk non-metastatic disease,[8] acceptance of this strategy requires confirmation through the performance of ongoing randomized prospective trials before this can be recommended to the general population. In retrospect, there have not been many substantive advances in chemotherapy for metastatic breast cancer since the development of doxorubicin and epirubicin.[9] While this situation may seem disheartening, newer developments have raised hopes that more effective chemotherapeutic agents may soon become available. The purpose of this article is to review these recent developments.

Drug development

This article will not review strategies for dose intensification, biochemical modulation or attempts to reverse drug resistance. Nor will it evaluate biological or hormonally-based approaches to control metastatic disease. It will therefore assess recent data on cytotoxic therapies. In this area, several promising new agents have recently been assessed including edatrexate (10-EDAM), losoxantrone (DUP-941), vinorelbine (navelbine), paclitaxel (taxol) and docetaxel (taxotere) (Figure 1). A brief outline of toxicities, pharmacokinetics and postulated mechanisms of action will be described for each agent, followed by a review of currently available phase II results and ongoing studies. Finally, an attempt will be made to explore what directions might be open to further clarify how these agents might be more fully evaluated and ultimately assessed in the adjuvant setting.

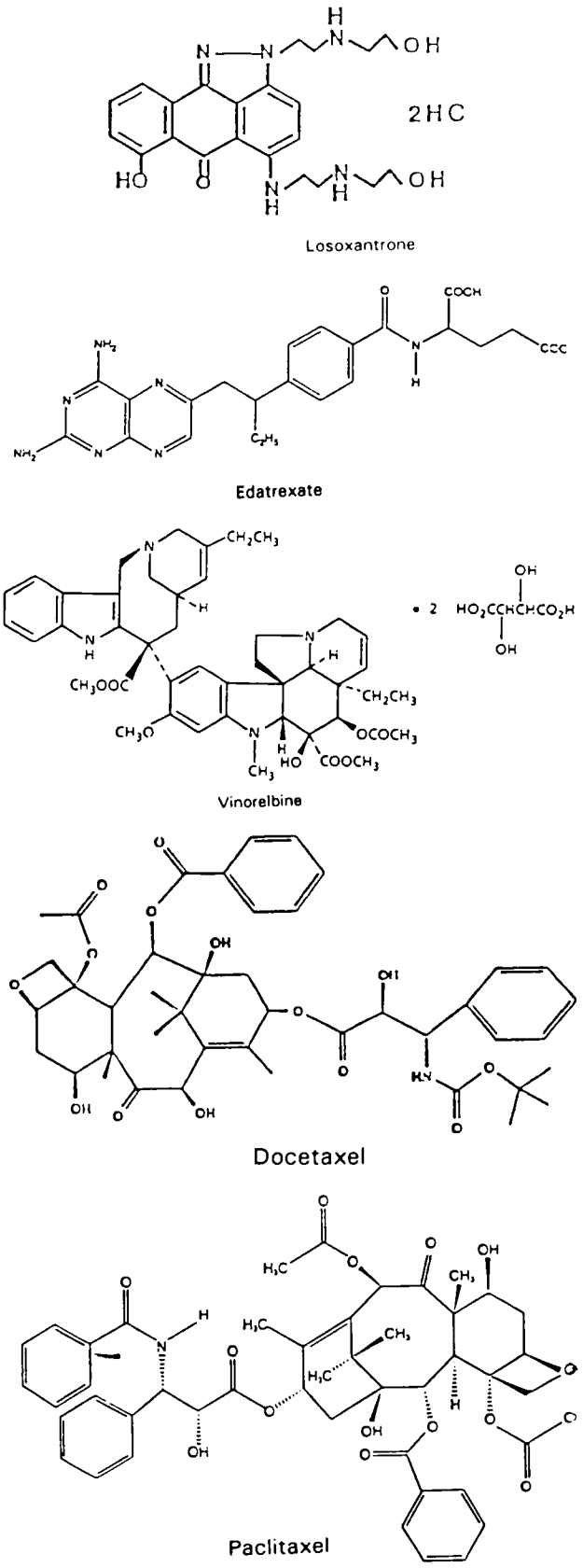

Figure 1. Promising new cytotoxics with activity in MBC.

Edatrexate

Edatrexate is a folate analog that competes for the folate binding site of the dihydrofolate reductase enzyme, inhibiting nucleotide and DNA synthesis. Preclinical studies have shown superiority compared to methorexate in terms of membrane transport and polyglutamylation.[10] The dose-limiting toxicity (DLT) in phase I studies has been mucositis. Other toxicities included leukopenia, thrombocytopenia, rash, alopecia, diarrhea and elevation of AST. It is metabolized in the liver and excreted mainly in bile.[11] All phase II studies have used a schedule of 80 mg/m^2/week. Two of these have been reported in metastatic breast cancer (MBC).[12,13] Both the Dutch and Canadian studies reported mucositis as the major DLT with the actual dose intensity delivered being 57 mg/m^2/week in the NCI Canada study. Although there were no episodes of febrile netropenia in the latter study, two patients developed pneumonitis secondary to therapy requiring hospitalization. Both cases were treated with corticosteroids and made a full recovery. Both studies reported a peculiar skin rash felt to be a toxic dermatitis which was successfully treated with corticosteroids. The Dutch study reported a significantly greater amount of toxicity including two deaths. This may be due to the older age in the latter study (median 67 versus 55 years). Response rates were 34 and 41%. Confirmatory studies are ongoing at the MD Anderson Cancer Center and the University of California Davis Cancer Center. Preliminary studies suggest that combinations of edatrexate with leucovorin, taxol, taxotere or cisplatin are worth further investigation and results may be schedule dependent for the taxanes.[14–16]

Losoxantrone

This anthrapyrazole is a DNA intercalator that does not undergo reduction in the presence of NADPH fortified microsomes or cytochrome P450 reductase and therefore is a potential non-cardiotoxic alternative to doxorubicin. It has shown less cardiotoxicity than doxorubicin in the fetal mouse heart model.[17] MTD in phase I studies has been leukopenia.[18] Three phase II trials have been undertaken to date.[19–21] All have used a schedule of 50 mg/m^2 every 3 weeks. The first, from the Royal Marsden Hospital, studied 31 patients with metastatic breast cancer, most of whom did not have prior chemotherapy for metastatic disease. None had any prior exposure to anthracyclines or mitoxantrone. The

other two studies which have just recently closed are part of a multicenter prospective phase II study evaluating this agent in patients with no prior exposure to chemotherapy for metastatic disease or one prior non-anthracycline containing regimen. Preliminary results have been published. DLT in all studies has been leukopenia but febrile neutropenia has not been a major problem to date. Nausea, vomiting and mucositis have been mild. No cardiotoxicity was reported in the first study but treatment was limited to nine courses. Possible cardiotoxicity is still being assessed from the multicenter study. The initial report showed substantial activity with an overall response of 63%. Preliminary results from the multicenter studies suggest overall responses of 30% in previously treated patients and 43% for patients without prior chemotherapy for metastatic disease. Further studies are planned.

Vinorelbine

This semisynthetic vinca alkaloid has been found in pre-clinical studies to have a higher tissue uptake than vinblastine.[22] Elimination is primarily via the biliary tree with a prolonged period of detection in the feces up to 3–4 weeks after administration.[23] Leukopenia is the DLT from phase I studies and neurotoxicity is mild to moderate.[24] Phase II studies have been conducted in Italy, France and Belgium, Latin America, Argentina, and Spain as well as a multicenter US study.[25–30] Moderate to severe alopecia, neurotoxicity or nausea and vomiting is uncommon. Responses have ranged from 24 to 52%. This agent has also been used in patients heavily exposed to prior anthracyclines and has shown significant activity [one complete response (CR) and eight partial responses (PR), 36% response] in this setting.[31] Combination studies with doxorubicin 50 mg/m^2 d1 and navelbine 25 mg/m^2 i.v. d1 and d8 showed a 21% CR rate and 66% overall response in 88 evaluable patients with no prior chemotherapy for metastatic disease.[32] A further study in a similar group of patients treated with Navelbine 30 mg/m^2 i.v. d1 and d5 along with 5-fluorouracil (5-FU) by continuous infusion d1–5 q3 weeks showed nine CRs and 10 PRs among 27 patients entered.[33] An oral formulation using liquid filled soft gelatin capsules seems to be tolerable but does cause increased gastrointestinal toxicity compared with the i.v. formulation. Antitumor activity has been noted in this setting.[34] A follow-up phase II multicenter trial of oral navelbine for MBC is active in the US. A phase III study in Argentina is randomizing patients between standard FAC chemotherapy (500/50/500 mg/m^2 q3w) and A (50 mg/m^2 q3w) + vinorelbine (25 mg/m^2 d1,8 q3w) in patients with no prior chemotherapy for MBC. Preliminary observations suggest an overall response of 75% for the vinorelbine + doxorubicin arm among the 45 patients evaluable to date and no difference in response or toxicity compared with standard treatment.[35] A randomized trial of doxorubicin versus doxorubicin plus navelbine is currently being carried out by the NCI Canada clinical trials group in patients with no prior chemotherapy for metastatic disease. Further studies by this same group are evaluating this agent with doxorubicin and 5-FU alone (FAN) or with the addition of leucovorin (superFAN).

Vinorelbine has been approved for use in France for the treatment of non-small cell lung cancer and breast cancer but has not yet been approved for use in the rest of Europe, North America or Japan. There are three reports of efficacy in patients who were heavily pretreated for metastatic disease. Marty reported a 36% overall response in 25 patients treated with prior chemotherapy regimens (88% prior anthracyclines). Apart from neutropenia there were no life-threatening complications.[36] Another study treated 50 patients of which 38 were evaluable for response and 48 for toxicity. Overall response was 24%. Venous toxicity required the placement of a central line in 30% of patients. Leukopenia was dose limiting. The planned dose was 30 mg/m^2/week but the dose intensity delivered was 70% of that originally intended.[37] The US multicenter study reported a 17% overall response in 41 evaluable patients.[30]

Paclitaxel

Paclitaxel (taxol) is a novel agent first derived from the bark of the Pacific yew tree (*Taxus brevifolia*). It acts to inhibit tubulin polymerization.[38] Therefore, in contrast to the vinca alkaloids that introduce microtubule disassembly, paclitaxel shifts the equilibrium to microtubule assembly and results in microtubules that are extremely stable.[39] Low concentrations also enhance the cytotoxicity of ionizing radiation.[40] Paclitaxel results in microtubule bundles that form during all phases of the cell cycle as well as mitotic asters not associated with centrioles. The fact that it is also inhibitory in non-mitotic phases suggests other mechanisms of action which remain unproven. This includes inhibition of disassembly of the interphase cytoskeleton and/or disruption of the tubulin cell membrane. Paclitaxel

has been shown to inhibit locomotion and shape changes of Walker 256 carcinosarcoma cells which may play a role in metastatic behavior.[41] Phase I trials were initially hindered by acute hypersensitivity reactions (HSRs) related to the cremaphore vehicle through the release of antihistamines.[42] This resulted in the application of 24 h infusion schedules along with premedication using dexamethasone, diphenhydramine and H2 antagonists. These measures have substantially reduced the incidence and severity of HSRs to about 3%. Neutropenia is the DLT in phase I trials using a 24 h infusion every 3 weeks. Nadirs occur at 8–11 days and myelotoxicity is not cumulative. Significant thrombocytopenia does not appear to be a major problem. Alopecia is extremely common, occurring suddenly and completely, and often causing loss of total body hair. Neurotoxicity is generally sensory, occurring in a symmetrical fashion in the extremities and sometimes causing perioral numbness. Severity is dependent on dose and cumulative exposure and usually precludes administration of amounts greater than 250 mg/m^2. Transient myalgias and arthralgias are mild at doses below 170 mg/m^2. Nausea, vomiting and diarrhea are generally not severe. Cardiac disturbances, with the exception of sinus bradycardia, are rare and usually not clinically significant.[43] A recent study conducted jointly by the NCI Canada and European investigators has shown, in a randomized trial comparing two different doses (135 and 175 mg/m^2) and schedules (24 and 3 h infusions) of paclitaxel in 275 evaluable patients with ovarian cancer, a very low 1.5% incidence of serious HSRs that was equal across all four treatment arms. In addition, there were fewer episodes of neutropenia and fever with the shorter infusion schedule.[44] The NCI and the CALGB plan a confirmatory prospective phase III study of these infusion schedules as second-line therapy in patients with metastatic breast cancer. Although biliary metabolites of paclitaxel have been identified, the fate of most of the administered dose has not yet been determined in man. Similarly, the impact of organ dysfunction on clinical toxicity has not been clearly assessed.[45] Different types of H2 blockers may have an impact on the steady-state concentration and clearance of paclitaxel but they do not seem to affect the severity of likelihood of neutropenia.[46] Chemotherapy sequencing may be important in combination studies. Mucositis is dose-limiting when paclitaxel infusion precedes doxorubicin in patients with breast cancer but not when the order of administration is reversed.[47] Paclitaxel administration prior to cisplatin results in decreased neutropenia and greater cytotoxicity *in vitro* against L1210 leukemia cells.[48,49]

Limited information is available regarding activity in chemotherapy naive patients with MBC. Phase II trials in patients have been completed at the MD Anderson Cancer Center and Memorial Sloan Kettering Cancer Center. The former studied 25 patients treated with 250 mg/m^2/24 h every 3 weeks.[50] All but two of them had prior exposure to doxorubicin and 11 received prior chemotherapy for metastatic disease. The overall response rate was 56% (12% CR) and two of six patients with doxorubicin resistant disease had a PR with paclitaxel. Response rates did not differ between groups with and without prior chemotherapy for metastases; 72% of patients required dose reductions, mainly for neutropenia; 44% of patients had fever or infection while neutropenic, 16% had grade 3 myalgia/arthralgia, 8% grade 3 neuropathy and 4% grade 3 diarrhea. The Memorial group studied 26 patients with no prior chemotherapy for metastatic disease.[51,52] Half had prior adjuvant exposure to doxorubicin. Treatment consisted of paclitaxel 250 mg/m^2/24 h and granulocyte colony stimulating factor (G-CSF) 5 μg/kg/day. Overall response was 62% (12% CR) including one CR and four PRs among eight patients with prior doxorubicin exposure. Of these patients, 21% required hospitalization for febrile neutropenia. In cycle 2, just over half of the patients had their doses reduced. Response duration data are not available for the MD Anderson or the Memorial studies as several of the patients have subsequently gone on to bone marrow transplantation or peripheral blood progenitor cell support programs in conjunction with high-dose consolidative chemotherapy. Single-agent results are now becoming available for patients with previous chemotherapy exposure in MBC. These include results from the MD Anderson Center, MSKCC, the NCI and a large multicenter study.[53–56] These results collectively suggest that approximately 25% of patients with anthracycline refractory breast cancer will respond to paclitaxel. The NCI study, using a 96 h continuous infusion, reported no allergic reactions despite the fact that none received any premedication. The multicenter study also suggests that anthracycline resistant disease may be sensitive to this drug even though half the patients received their treatment as a 3 h infusion; 77% of patients had prior anthracycline exposure in this trial. Of interest is the finding that cremophore EL has been reported to reverse multidrug resistance.[57] Combination studies are now underway, evaluating the efficacy and toxicity of paclitaxel and doxorubicin, cyclophosphamide

or cisplatin. There is also a phase II randomized study of doxorubicin versus paclitaxel with a cross-over for treatment failures being conducted by the EORTC. A randomized phase III trial of four doses of paclitaxel is planned by the CALGB. ECOG has activated a phase III trial comparing doxorubicin versus paclitaxel versus paclitaxel/doxorubicin/G-CSF in patients with MBC

Docetaxel

Docetaxel (taxotere) is a semi-synthetic compound obtained from the needles of the European yew tree (*Taxus baccata*). It acts similarly to paclitaxel and has been in phase I development since 1990.[58,59] This agent has shown enhanced *in vitro* and *in vivo* antitumor activity in preclinical models compared with taxol.[60,61] Myelosuppression is the main DLT. Other significant toxicities that have been reported include stomatitis which is less severe on the q 3 week schedule and asthenia. The skin toxicity, which is more peculiar for docetaxel than paclitaxel, can consist of localized palmar–plantar erythema, occasionally progressing to desquamation, nail changes and a maculo-papular rash. Nausea, vomiting and diarrhea are usually mild. Hypersensitivity reactions are generally less severe than with paclitaxel. Alopecia is common. There has been no significant cardiac toxicity and minimal thrombocytopenia reported in phase I trials.[62–65] Four groups have reported results in previous chemotherapy naive MBC.[66–69] This appears to be an extremely active agent with response rates approaching 60–70%. Reported toxicities from these studies include hypersensitivity reactions which can be attenuated with premedication regimens similar to that used for paclitaxel. The EORTC has activated a phase II study evaluating the effectiveness of antihistamines with or without methylprednisolone in preventing hypersensitivity reactions and skin toxicity. The EORTC clinical screening group reported that 12 of 24 responding patients developed effusions/edema. A phase I trial from San Antonio has also reported pleural effusions in three of six patients treated.[70] The reason for this problem is unclear but it seems to occur after four or more courses of treatment. The MD Anderson Cancer Center has reported the first results using taxotere in patients with MBC refractory to doxorubicin. This early study reports four PRs in six patients evaluable for response. One patient died from neutropenic sepsis. Granulocytopenia was severe but, to date, non-hematologic toxicity has been tolerable.[71] No studies employing docetaxel in combination with other agents have yet been activated.

Other drugs

Difluorodeoxycytidine (gemcitabine) has shown activity in patients with MBC. One study has reported a response rate of 29% in the 35 of 44 patients evaluable. Seven of the inevaluable patients pro-

Table 1. Phase III results in patients with no prior chemotherapy for metastatic disease

Drug	Study	Patients evaluable	Dose and schedule	Response		
				CR	PR	%
Edatrexate	Netherlands	32	80 mg/m^2/w	3	8	34
	NCI Canada	32	80 mg/m^2/w	2	11	41
Losoxantrone	Royal Marsden	30	50 mg/m^2/3 w	2	17	63
	Multicentre	44	50 mg/m^2/3 w	1	19	43
Navelbine	Italy	19	30 mg/m^2/w			52
	Latin America	44	30 mg/m^2/w	3	20	52
	France/Belgium	145	30 mg/m^2/w	10	50	41
	Spain	47	30 mg/m^2/w	2	7	24
	Argentina	20	30 mg/m^2/w	1	9	50
	Multicenter US	65	30 mg/m^2/w	10	16	40
Taxol	MD Anderson[a]	14	250 mg/m^2/3 w	2	6	57
	MSKCC	26	250 mg/m^2/3 w	3	13	62
Taxotere	EORTC-CSG	32	100 mg/m^2/3 w	6	18	72
	MSKCC	14	100 mg/m^2/3 w	2	6	57
	NCI Canada	49	100 mg/m^2/3 w	5	25	67
	EORTC-ECT group[b]	24	100 mg/m^2/3 w	2	7	40

[a]Patients with prior chemotherapy removed from analysis.
[b]Early results—four patients with measurable PR but not yet 4 weeks out.

gressed prior to receiving two courses of therapy. Most had received prior chemotherapy for MBC. This agent was well tolerated and the most common toxicity was lethargy. Nausea, vomiting, alopecia and myelosuppression were mild.[72] This drug requires further evaluation, particularly in chemotherapy naive MBC.

Table 3. Known factors influencing response to therapy in MBC

Time from diagnosis to recurrence
Prior chemotherapy
Response to prior chemotherapy
Sites of disease
Number of disease sites
Performance status
Single versus multiple institution trial

Discussion

The overall antitumor effects in phase II studies are presented in Tables 1 and 2 for chemotherapy naive and more heavily pretreated MBC, respectively. These studies generally show moderate to very good activity against disease but their confidence levels have considerable overlap because of the small numbers of patients studied. Evaluation of any new treatment requires an adequate description of the population studied, the dose, schedule and actual dose intensity of treatment given, and standardized outcome assessment. These outcomes should include complete and partial responses, duration of response, median survival and toxicity. Nevertheless, there is still considerable heterogeneity to be found in the MBC patient population which can affect the likelihood of response to treatment (Table 3). Clinicians have become more sensitive to the importance of standardized outcome measures.[73] However, difficulties persist in this regard. Different institutions and cooperative groups have differing definitions of response during duration (time from initiation of treatment versus time from documentation of initial response) or use other terms such as time to progression or time to relapse. Some centers will place responding patients on other treatments such as autologous bone marrow transplant or peripheral blood progenitor cell high-dose chemotherapy protocols. These centers will not be able to provide data about response duration. Definitions of resistance to therapy vary from progression while on treatment to progression within 6 months to 1 year after stopping treatment. Many single-center trials may only be published in abstract form, or not at all, particularly if they are negative studies, resulting in publication bias in the reporting of overall results. Multicenter phase II studies are a more accurate way of determining activity in a less preselected patient population and also offer more cancer patients the opportunity to participate in clinical trials. This requires adequate support of research infrastructure to ensure that the quality of data collected is appropriate to the era of good clinical research practice. Multicenter trials are also becoming a more effective way of ensuring efficient patient accrual. Quality of life tools are increasingly utilized in phase III trials and may provide useful information that toxicity assessments cannot.

We are now at an exciting point in the development of newer therapies for MBC. Ultimately, decisions on what treatments to pursue will require direct prospective randomized comparisons. These could occur in the setting of first line therapy for MBC but might be more usefully studied in patients failing anthracycline therapy for metastatic disease to determine which would have the least cross-

Table 2. Phase II results in patients with no prior chemotherapy for metastatic disease

Drug	Study	Patients evaluable	Dose and schedule	Response		
				CR	PR	%
Taxol	MD Anderson	12	150 mg/m^2/3 w	0	3	25
	MSKCC	72	250 mg/m^2/3 w			28
			200 mg/m^2/3 w			
	NCI	17	140 mg/m^2/96 h	0	9	53
	Multicenter	58	135 mg/m^2/3 w			22
		59	175 mg/m^2/3 w			29
Taxotere	MD Anderson	6	100 mg/m^2/3 w	0	4	67
Vinorelbine	ARTAC	38	30 mg/m^2/w	2	7	24
	Paris	25	30 mg/m^2/w	1	8	36
	Multicenter US	41	30 mg/m^2/w	1	6	17

resistance. Given the significant impact of this disease, a series of prospective multicenter trials should be considered a priority so that the best agents can be identified for adjuvant trials.

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