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Cytotoxic Agents with Activity in Breast Cancer Patients Previously Exposed to Anthracyclines: Current Status and Future Prospects

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INTRODUCTION

THE NATURAL history of metastatic breast cancer has changed very little over the last 15 years. Following failure with hormonal manipulation, combination chemotherapy results in 60–70% objective responses, with at best a quarter being classified as complete. The median duration of response is usually in the range of 8–12 months and the median survival about 24 months [1, 2]. Second-line chemotherapy, with currently available agents, is effective in only half the patients who have responded to the first-line regimen and in only one third of the overall population; here, median response duration is usually around 4 months and median survival rarely exceeds 8–9 months [3].

Efforts to study combinations of hormonal agents with chemotherapy [4], rotation of chemotherapy regimens [5], or more recently high dose chemotherapy, with or without the support of autologous bone marrow transplantation or peripheral blood progenitor cells [6–12], have sometimes been gratifying in terms of response rates but very rarely in terms of long term survival. Anthracyclines are considered to be the most active agents presently available in advanced breast cancer, with response rates ranging from 20 to 75% [13–25]. Also, there is evidence for a dose–response relationship, especially in chemotherapy-naïve patients [26–28]. Their incorporation into combination regimens has provided a modest but definite improvement in response rates, but their prolonged use remains limited due to the cumulative cardiotoxicity [29, 30].

A particularly difficult clinical situation involves patients found to be "resistant" to anthracycline-based chemotherapy: indeed, therapeutic options are very limited for these patients and they are known to have a very poor prognosis [31, 32]. Despite medical oncologists' growing interest in molecular mechanisms underlying drug resistance, and the clear perception that new drugs active in anthracycline resistance are urgently needed, there are few clinical studies addressing this issue prospectively. We have attempted to review the activity of a number of old and new cytotoxic drugs, alone or in combination, in the setting of "anthracycline-resistant" breast cancer. We have *a priori* defined four potential categories of patients, reflecting varying degrees of anthracycline resistance, the least controversial being the first.

(1) Patients progressing on anthracycline-based chemotherapy, without experiencing any transient improvement.
(2) Patients whose disease remains stable after administration of a minimum of four cycles of anthracycline-based chemotherapy.
(3) Patients relapsing within 6 months of the completion of an anthracycline-based adjuvant chemotherapy regimen.
(4) Patients experiencing a brief objective response to anthracycline-based chemotherapy with subsequent progression while on the same therapy.

Of note, all these operational definitions of "anthracycline resistance" also imply the administration of a minimum dose of anthracycline: 50 mg/m^2 doxorubicin in combination therapy and 60–75 mg/m^2 doxorubicin used as a single agent. With these definitions in mind, the activity of the following compounds has been reviewed: 5-fluorouracil (5-FU) as a low dose continuous infusion, platinum drugs, vinorelbine, paclitaxel and docetaxel. In addition, four newer compounds, or families of compounds, namely Gemcitabine®, anthrapyrazoles, edatrexate and camptothecins, which are still in an early clinical development phase, will be briefly discussed.

5-FLUOROURACIL LOW DOSE CONTINUOUS INFUSION

5-FU has been used extensively for 30 years, and it remains one of the reference drugs in breast cancer chemotherapy. In an overview of 1263 patients with advanced breast cancer, the response rate to single-agent 5-FU administered by intravenous bolus injection was 26% [33]. In the last 10 years, the modulation of 5-FU intracellular pharmacology through biochemical or scheduling manipulations has resulted in benefits in therapeutic index, and substantial changes in response rate and quality of response in colorectal cancer. These results highlight the following points:

(1) Modulation of 5-FU pharmacology in some highly chemotherapy-resistant cancers improves its therapeutic index.
(2) The improvement in the therapeutic index appears to be

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partly due to a change in toxicity, especially in the case of continuous administration which shows little myelosuppression and has a dose-limiting toxicity of stomatitis and/or diarrhoea and/or plantar-palmar erythema.

Randomised trials in metastatic colorectal cancer have demonstrated superior response rates with 5-FU given as continuous infusion or in combination with folinic acid, as compared to bolus injection. Recently, Falcone and associates reported incomplete clinical crossresistance between 5-FU bolus injection and continuous infusion in metastatic colorectal cancer patients [34].

Unfortunately, in breast cancer, 5-FU has been given primarily as a bolus injection without any biochemical modulation in conventional combinations. There is no doubt that this method of administration is suboptimal and it is possible that the therapeutic index may be increased in breast cancer through folinic acid-based combinations or by continuous infusion administration.

Preclinical data

The antimetabolite 5-FU exerts its antitumour effects through its metabolic conversion to nucleotide derivatives such as 5-fluorouridine 5′-triphosphate, which is incorporated into RNA, and 5-fluorodeoxyuridylate, which inhibits thymidylate synthetase and thereby DNA synthesis [35–37]. The cellular sensitivity to 5-FU can be determined by several factors including intracellular drug levels, the activity of the enzymes involved in its uptake and metabolism, as well as pre-existing levels of nucleotide pool [38–40]. 5-FU has a short serum half life due to rapid catabolism [41, 42]. More than a decade ago, *in vitro* studies using a variety of human epithelial cancer cell lines addressed the issue of a schedule dose relationship of 5-FU cytotoxicity: they showed that low dose prolonged exposures were able to minimise sensitivity variations resulting from different rates of drug uptake and metabolism, as well as cell cycle times [43]. These properties support a rationale for using continuous infusions of 5-FU in unfavourable clinical circumstances such as the development of 5-FU bolus and/or anthracycline resistance.

Clinical data

Table 1 summarises the results obtained with single agent continuous infusion 5-FU in metastatic breast cancer previously exposed to chemotherapy. The response rate ranges from 12 to 53% with a median duration of 2–6 months [44–50]. The majority of patients were heavily pretreated and were refractory to most of the cytotoxic drugs available, including 5-FU bolus combination chemotherapy. Although a high proportion had received anthracyclines, the published reports do not contain the information needed in order to classify the patients in one of the four "resistant" subsets defined above.

The toxicity profile of 5-FU administered by continuous infusion appears to be acceptable, with primary toxicity being the hand–foot syndrome [44–50]. The rather favourable therapeutic index of this treatment modality makes it an attractive candidate for a prospective trial in patients "resistant" to anthracyclines.

PLATINUM COMPOUNDS

In spite of the fact that cisplatin is clearly an active agent in breast cancer, with response rates around 50% when the drug is given at relatively high dosages in chemotherapy-naïve patients [51–53], it has not made the same impact on the treatment of this disease as it has on the therapy of ovarian cancer. Carboplatin, the only platinum analogue widely used in oncology thus far, appears to be less active against breast cancer than the parent drug [54, 55], and its increased myelotoxic properties complicate its use in combination with other drugs. There are, however, preclinical and clinical data suggesting that old or newer platinum compounds may find a "niche" in the management of anthracycline-resistant breast cancer.

Preclinical data

The mechanisms of resistance to cisplatin, which have been studied extensively in ovarian cancer cell lines, clearly differ from those involved in anthracycline resistance: they include increased total DNA repair, DNA sequence-specific interstrand crosslink removal and increased drug inactivation by glutathione (GSH) [56].

Carboplatin is largely crossresistant with cisplatin. In contrast, the new platinum compound, oxaliplatin, is active against several

Table 1. Phase II single agent studies with 5-FU low dose continuous infusion in patients with advanced breast cancer previously treated with chemotherapy

Authors	Ref.	No. of evaluable patients	No. with prior anthracycline exposure	Median no. of prior CTX regimens	Median WHO PS	% CR+PR	Median duration of response (months)
Huan *et al.*	[44]	28	22	2	2	53	4*
Jabboury *et al.*	[45]	32	32	4	3	16	4
Hansen *et al.*	[46]	25	20	4	2	32	6
Lokich and Anderson	[47]	33	NA	3	NA	14	NA
Chang *et al.*	[48]	10	2	2	2	40	NA
Berlie *et al.*	[49]	33	NA	≥1	NA	12	NA
Izzo *et al.*	[50]	14	NA	≥1	NA	23	<2
Total		175				23% (range 12–53)	2–6 months

*No details given on the behaviour of the tumour under anthracycline treatment. CR, complete response; CTX, chemotherapy; NA, not available; PR, partial response; PS, performance status.

Table 2. Cisplatin-based combination regimens in patients with advanced breast cancer previously treated with chemotherapy

Regimen	Authors	Ref.	No. of patients/ evaluable	No. with prior anthracycline exposure	No. CR+PR	Median duration of response	Median time to progression
Cisplatin + etoposide	Cox *et al.*	[66]	31/29	31	11	CR = 35 w PR = 17 w	NA
	Cocconi *et al.*	[67]	30/24	24	4	17 w	NA
	Krook *et al.*	[63]	44	13	11	NA	4 m
	Tinsley *et al.*	[68]	42	NA	7	2.5 m	3.3 m
	Total		139		33 (24%)		
Cisplatin + vindesine	Paridaens *et al.*	[69]	46		9 (19%)	5 m	NA
Cisplatin + 5-FU	Fumoleau *et al.*	[62]	30/27	30	8	4.2 m	NA
	Fernandez Hidalgo *et al.*	[70]	23	16	11	8 m	NA
	Bitran *et al.*	[71]	24	24	12	4.9 m	4.6 m
	Jacobs *et al.*	[72]	14	NA	5	NA	NA
	Pronzato *et al.*	[73]	15	NA	2	NA	NA
	Total		103		38 (37%)		

CR, complete response; m, months; NA, not available; PR, partial response; w, weeks.

cell lines resistant to cisplatin and carboplatin [57–61]. One possible explanation could be the kinetics of oxaliplatin reaction with DNA, which is far more rapid than with either cisplatin or carboplatin: the formation of DNA adducts is nearly complete within 15 min, whereas this process peaks at approximately 12 h for cisplatin and over 24 h for carboplatin [57, 58].

Clinical data

When cisplatin or carboplatin is given as single agent to breast cancer patients previously treated with chemotherapy, the response rate is disappointingly low, in the range of only 0–10% [62]. Their use in combination with 5-FU, etoposide or vindesine, after failure of chemotherapy regimens which often contained anthracyclines, is more encouraging: response rates, which are summarised in Tables 2 and 3, range from 5 to 38%, with response durations around 4 to 5 months for cisplatin-containing regimens, and somewhat shorter for carboplatin-based combinations.

Unfortunately, previous response to anthracyclines in these various phase II trials [63–76] has not been well characterised: as a result, the real potential for such combinations to overcome anthracycline resistance will require prospective evaluation. Of note, the toxicity associated with these platinum-based regimens is not mild, and includes substantial gastrointestinal toxicity, fatigue and, sometimes, pronounced myelosuppression.

So far, only 12 patients with heavily pretreated breast cancer have been treated with oxaliplatin: an objective response was observed in 5. This new promising platinum compound, which lacks renal toxicity and significant myelosuppression, has moderate gastrointestinal side-effects and is associated with a dose-limiting peripheral sensory neuropathy [77], deserves further testing in advanced breast cancer, including anthracycline-resistant disease.

Table 3. Carboplatin-based combination regimens in patients with advanced breast cancer previously treated with chemotherapy

Regimen	Authors	Ref.	No. of patients/ evaluable	No. with prior anthracycline exposure	Median no. of prior CTX regimens	Median WHO PS	No. CR+PR (%)	Median duration of response	Median time to progression
Carboplatin + etoposide	Vinolas *et al.*	[74]	27	13	NA	0–1	5 (18.5)	10 w	26 w
Carboplatin + 5-FU	Fiorentino and Brandes	[75]	32/28	27	3	0–1	12 (42)	7 m	2 m
	Palacio *et al.*	[76]	21/19	19	1	NA	1 (5)	NA	

CR, complete response; CTX, chemotherapy; m, months; NA, not available; PR, partial response; PS, performance status; w, weeks.

VINORELBINE (NAVELBINE®)

Vinorelbine or 5'nor-anhydrovinblastine (Navelbine®) is a semisynthetic vinca-alkaloid currently registered for use in advanced breast carcinoma and non small cell lung cancer in many countries in Europe and South America. Similarly to the other vinca-alkaloids, it binds to tubulin and blocks polymerisation of microtubules, resulting in mitotic spindle dissolution and metaphase arrest in dividing cells [78, 79].

Single agent activity of vinorelbine, when given as first-line chemotherapy for metastatic breast cancer, is reported to be in the range of 40–52% [80–84], with reasonable response durations (50–73 weeks) and, above all, a favourable toxicity profile including easily manageable neutropenia, little alopecia and mild to moderate neurotoxicity. However, phlebitis is reported in up to one third of patients, often necessitating the use of venous access devices. Some preclinical and clinical data suggest that this drug may play a role, although probably modest, in the management of the anthracycline-resistant breast cancer patients.

Preclinical data

There has been an attempt over the last 3–4 years to characterise the vinorelbine resistance phenotype and the potential activity of the drug against cell lines with elevated P-glycoprotein [85–87]. The preliminary conclusions so far are that, although resistance to vinorelbine often appears to involve "mdr", it may also be related to cytoskeleton or DNA-directed mechanisms. These observations would suggest that anthracycline resistance and vinorelbine resistance may not always evolve in parallel.

Clinical data

Table 4 gives an overview of the single agent activity of vinorelbine in patients who have failed at least one regimen for advanced disease. Nine trials have been conducted, eight as open phase II studies and the last one as a randomised comparison against intravenous melphalan. Intended dosages of weekly intravenous Vinorelbine have ranged from 20 to 30 mg/m^2.

In the first five trials [88–91, 84] (Table 4), information on prior anthracycline exposure was not detailed, but the last four studies [92–95] enrolled only patients previously treated with anthracyclines, either in the adjuvant setting or at the time of relapse. Unfortunately, as some papers are only available in abstract form, there is little information on the response or the disease-free interval following anthracyclines and, therefore, true anthracycline resistance in these patients cannot be ascertained.

As can be seen in Table 4, the objective response rate in these trials ranges from 15 to 48%. Information on response duration or time to progression is rarely available. Degardin and colleagues state that "there was no significant difference in response rate whether patients responded previously to anthracyclines or not" [93]. The higher response rate observed by Barni and associates [92] may have been related to a higher proportion of patients with dominant soft tissue disease as opposed to visceral disease.

TAXOID COMPOUNDS

Paclitaxel (Taxol®) and docetaxel (Taxotere®) are two drugs belonging to a new class of cytotoxic agents with a unique mechanism of action, consisting of the stabilisation of intracellular microtubules and inhibition of their depolymerisation [96]. Paclitaxel is currently registered for clinical use in ovarian cancer patients failing platinum compounds, in North America and in Europe, and in breast cancer patients failing anthracycline-based chemotherapy in North America. Docetaxel has recently been submitted for registration review in breast and non small cell lung cancer in Europe and North America.

When paclitaxel is given at the relatively high dosage of 250 mg/m^2 as a 24 h infusion with granulocyte-colony stimulating factor (G-CSF) support or when docetaxel is given at its maximum tolerated dose of 100 mg/m^2 as a 1 h infusion to advanced breast cancer patients who have had either no prior chemotherapy or only adjuvant chemotherapy with a disease-free interval of at least 1 year, the response rate observed is high, in the range of 55–76% [97–100]. The growing interest in taxoid compounds for the management of breast cancer patients lies

Table 4. Vinorelbine single agent activity in patients with advanced breast cancer previously treated with chemotherapy

Authors	Ref.	Dose and schedule	No. patients/ evaluable	Median no. of prior CTX regimens	Median WHO PS	CR+PR (% confidence intervals)	Median duration of response	Median time to progression
(A) Reports with a lack of information regarding prior anthracycline exposure								
Marty *et al.*	[88]	30 mg/m^2/week	33	1–2	<2	33 (14–49)	21 w	NA*
Roché *et al.*	[89]	30 mg/m^2/week	46	1	NA	20 (10–38)	14 w	NA
Weber *et al.*	[84]	30 mg/m^2/week	41	1	NA	17 (NA)	34 w†	NA
Demicheli *et al.*	[90]	30 mg/m^2/week	20/16	≥1	0–1	56 (30–80)	NA	NA
Gasparini *et al.*	[91]	20–25 mg/m^2/week	70/67	2	1	36 (24–47)	NA	18 w
(B) Reports in patients who have all received prior anthracyclines								
Barni *et al.*	[91, 92]	20 mg/m^2/week	30	≥1	1	33 (NA)	NA	NA
Degardin *et al.*	[93]	30 mg/m^2/week	109/100	≥1	1	16 (8–23)	20 w	NA
Dogliotti *et al.*	[94]	30 mg/m^2/week	48/44	1	1	21 (NA)	NA	NA
Jones *et al.*	[95]	30 mg/m^2/week	115	1 or 2	1	15 (NA)	NA	12 w

*Most reports are published only in abstract form; † only for complete responders. CR, complete response; CTX, chemotherapy; NA, not available; PR, partial response; PS, performance status; w, weeks.

mainly in their level of activity in heavily pretreated patients, and in their potential for overcoming anthracycline resistance.

Preclinical data

The identification of mechanisms of resistance to taxoid compounds is under intense investigation. Development of resistance to paclitaxel *in vitro* can be related to amplification of multidrug resistance (MDR) genes and/or overproduction of tubulin, as shown by Horwitz in a macrophage cell line made resistant to paclitaxel *in vitro* [101]. The observation that docetaxel is 4-fold less crossresistant than the parent drug on the P388 cell line, which is resistant to doxorubicin, is interesting: this cell line has been shown to overexpress the *MDR* gene and to have altered topoisomerase II activity [102]. Another finding of interest, because of its potential clinical relevance, is the fact that long term exposure to paclitaxel *in vitro* markedly increases cytotoxicity, and has the potential to overcome P-glycoprotein mediated multidrug resistance [103].

Additional studies are needed to clarify the molecular basis for taxoid and anthracycline resistance, and to verify the partial non crossresistance between taxoid compounds and anthracyclines and between paclitaxel and docetaxel. Also, the intriguing observation that Cremophor EL can reverse drug resistance and has activity on its own on doxorubicin-resistant human breast cancer cell lines is worth mentioning [104]. Paclitaxel (but not docetaxel) is indeed formulated in Cremophor EL.

Clinical data

As can be seen in Table 5, which summarises current knowledge on the activity of taxoid compounds in patients considered as "resistant" to anthracyclines, there is still some degree of uncertainty concerning the optimal dose and schedule of drug administration with paclitaxel. The principle toxicity, neutropenia, is strongly schedule-dependent and this favours the use of a short, 3 h infusion; however, resistance can develop on the 3 h schedule and a prolonged infusion might overcome it. Doses used vary between 135 and 250 mg/m^2, with the addition of G-CSF (granulocyte colony stimulating factor) support for the higher doses. With docetaxel, the situation is less complex and the drug is given at a dose of 100 mg/m^2 as a 1 h infusion. Neutropenia has not been found to be schedule-dependent in the various phase I studies of docetaxel, and the 1 h administration every 3 weeks was associated with the highest dose intensity [96].

Only one paclitaxel study has been designed to focus specifically on "anthracycline-resistant" patients, the study of the European Cancer Center in Amsterdam by Vermorken and colleagues [107]. In looking retrospectively into the data generated by the Gelmon study [105] and a trial by the Memorial Sloan-Kettering Hospital group [106], the latter being conducted in a heavily pretreated patient population previously exposed to a median of two chemotherapy regimens, definite although modest antitumour activity can be demonstrated for paclitaxel in the anthracycline-resistant subsets defined previously (Table 5). However, the response rate of 6% (95% CI 0–14) in the more strictly defined patient population of Vermorken is somewhat disappointing, since a high dose of paclitaxel with G-CSF support was selected. Because of the concern that paclitaxel's activity might be schedule-dependent, a prospective trial of prolonged paclitaxel infusion in anthracycline-resistant breast cancer appears warranted.

In the clinical development of docetaxel, three studies have been specifically designed to assess the drug's activity in "anthracycline-resistant" patients: two in the U.S.A. [108, 109] and one in Europe [110]. The European trial has used stricter definitions of "anthracycline resistance" in its eligibility criteria, allowing inclusion of patients belonging to subsets 1 and 2 defined above (subsets 3 and 4 were not eligible). This multicentric trial has recently closed after accrual of 51 patients. The MD Anderson study (updated FDA efficacy summary and [108]) accrued 41 patients of whom 35 were anthracycline-resistant (5 others being mitoxantrone-resistant and 1 not resistant): 17 responses were observed (48%; 95% CI 32–65) including 6/16 responses in the worst subsets with primary resistance (i.e. progression on adjuvant therapy or progressive disease as best response to chemotherapy for advanced disease). This impressive antitumour activity has been confirmed in the second American trial conducted at the University of Texas Health Science Center in San Antonio [109]: the objective response rate was also 48% (95% CI 28–68) in 25 evaluable patients.

The response rate in Marty's trial is somewhat lower (29%; 95% CI 16–41), but this trial did not allow for recruitment of patients progressing on anthracyclines after an intervening response.

The data available so far on taxoid compounds point to a real potential for these drugs, and particularly for docetaxel, to impact on the poor natural history of anthracycline-resistant breast cancer. A prospective, randomised, clinial trial might help identifying which of the two taxoids has the most favourable therapeutic index in this clinical situation.

NEW COMPOUNDS

Four new drugs or classes of drugs are undergoing early evaluation in breast cancer. Because very few patients with anthracycline-resistant disease have been studied so far, only overall results can be presented. Gemcitabine® is a pyrimidine analogue with activity in a number of experimental solid tumour systems. In phase I trials, several schedules were tested, and 800 mg/m^2 intravenously weekly ×3 every 4 weeks was selected for phase II evaluation. Carmichael and associates have carried out a trial in women with metastatic breast cancer who have had up to one prior chemotherapy regimen [111]. Among 35 patients evaluable, 9 (26%) had an objective response. 5 responders had received prior chemotherapy and 4 had liver involvement. No information is available on what proportion had received or progressed on anthracyclines prior to Gemcitabine® treatment. Toxic effects with this dose and schedule of Gemcitabine® were modest.

Anthrapyrazoles are a new group of compounds based upon modification of the chromophore nucleus of anthracenediones. Like anthracyclines, they act by interaction with DNA topoisomerase II, but in experimental systems produce less cardiotoxicity. Only one anthrapyrazole, DUP 941 (losoxantrone) has been studied in breast cancer. Talbot and colleagues observed a 63% response rate when losoxantrone 50 mg/m^2 every 3 weeks was given to 30 patients with metastatic breast cancer [112]. While 52% of patients had received prior chemotherapy, none had received anthracyclines. In a larger trial reported this year by Calvert and colleagues, 207 patients (188 evaluable) received the same dose and schedule of losoxantrone. Almost half had had previous chemotherapy but prior anthracycline exposure was an exclusion criterion. The response rate in the second trial was 39%. Grade 3 neutropenia was common but other effects were generally mild or moderate in severity [113].

Edatrexate is a methotrexate analogue which was selected for clinical development because of enhanced activity in some

Table 5. Taxoid studies in patients pretreated with anthracyclines: antitumour activity in patients considered as "resistant to anthracyclines"

	Paclitaxel studies			Docetaxel studies			
Type of study	Seidman *et al.* [106] Unicentric	Gelmon *et al.* [105]* Multicentric, randomised for dose		Vermorken *et al.* [107] Unicentric	Valero *et al.* [108] Unicentric	Ravdin *et al.* [109] Unicentric	Marty *et al.* [110] Multicentric
Taxoid dose [mg/m²]/schedule	200/24 h	175/3 h	135/3 h	250–300/3 h	100/1 h	100/1 h	100/1 h
Prophylactic G-CSF support	Yes	No	No	Yes	No	No	No
Routine premedication	Yes	Yes	Yes	Yes	Yes	Yes	Yes
No. patients pretreated with anthracyclines	29	152	151	36	41	42	51
No. patients defined as resistant to anthracycline	20	38	30	33	35	25	49
Response/anthracycline-resistance subset							
Relapse ≤6 m post adjuvant†	0/1	3/8	0/4	–	2/3	1/2	1/5
Best response to anthracyclines for locally advanced or metastatic disease = progressive disease	2/11	8/30	4/26	0/10	4/13	5/15	9/25
Stable on anthracyclines	4/8	–	–	1/13	11/19	6/8	4/19
Initial response to anthracyclines followed by PD on athracyclines	–	–	–	1/10			–
Total no. of objective responses (%)	6/20 (30)	11/38 (29)	4/30 (13)	2/33 (6)	17/35 (48)	12/25 (48)	14/49 (29)
% Response rate (95% CI)	30 (10–50)	29 (15–43)	13 (1–25)	6 (0–14)	48 (32–65)	48 (28–68)	29 (16–41)

*These are updated data presented at the 1994 NCI–EORTC Symposium on New Drugs in Cancer Therapy (total accrual = 454 patients); † Includes a few relapses on adjuvant chemotherapy for the paclitaxel study and exclusively relapses on adjuvant chemotherapy for the docetaxel trials.

experimental tumour models. Weekly edatrexate 80 mg/m^2 intravenously has been studied in two trials in metastatic breast cancer. Schornager studied 32 patients with no prior chemotherapy and observed a 34% response rate [114]. Vandenberg and associates, who also studied 32 patients, 12 with prior adjuvant chemotherapy, reported a 41% response rate (64% in those with prior chemotherapy). Treatment was limited by mucositis and skin rash [115].

The final class of compounds of interest are the camptothecins which are inhibitors of topoisomerase I. Four analogues are now undergoing clinical evaluation, but only limited data are available in breast cancer. Bonneterre and colleagues studied irinotecan (CPT-11) in 12 patients with breast cancer and documented one complete response. That study has not yet been reported in final form [116]. Taguchi and associates carried out a trial of irinotecan in Japan and reported a 23% response rate in 65 evaluable patients, 46 of whom had had prior chemotherapy [117]. A trial of topotecan is ongoing in the U.S.A. Results have not yet been reported, but will be of interest because the investigator is correlating tumour response with pretreatment topoisomerase I tumour levels.

In summary, of the four compounds/classes discussed, both Gemcitabine® and the camptothecins would be of interest to study further in an anthracycline-resistant population of patients. Neither are likely to be affected by the resistance mechanisms which are thought to be important in this setting. Edatrexate is less interesting since it is an analogue of an agent already in use, and its toxic effects will make it difficult to use in combination. Anthrapyrazoles are the least likely to be active in anthracycline resistance because their mechanism of action and chemical structure are so similar.

DISCUSSION

Since the use of combination chemotherapy and the introduction of doxorubicin in 1974, there have been no additional gains in survival for metastatic breast cancer patients. It is likely that progress will occur if therapeutic modalities active in anthracycline-resistant disease are identified. As there is not a widely accepted definition of "anthracycline resistance", we should be cautious when using this term without further specification. The use of simple, operational definitions of "resistant" patients subsets should be encouraged, as these would facilitate the identification of drugs or treatment modalities which have the potential to improve today's management of the "resistant" patient. It would also facilitate our ability to interpret the results of clinical trials which purport to have been undertaken in anthracycline-resistant disease.

This review stresses the urgent need for better characterisation of breast cancer patient populations treated in phase II trials. From the available literature, it is impossible to obtain adequate information on prior treatment such as drugs used, dosages given and "clinical sensitivity" or "resistance" to these drugs. As a result, it is extremely difficult to identify which of the drugs currently available should be tried as a priority once anthracycline resistance becomes evident. Also, the major emphasis is on "response rates" while information on other important endpoints such as response duration, time to progression, symptom relief is very often lacking. From the data presented in this review of "anthracycline-resistant breast cancer", it would appear that the therapeutic index of navelbine or platinum-based combinations is quite modest, that the prolonged low-dose 5-FU infusion should be re-explored since it seems to combine reasonable antitumour efficacy with mild toxicity and that taxoid compounds offer, so far, the greatest hope. Their toxicity, however, can be significant, and, therefore, a continued search for new drugs, active in this setting, should be pursued.

The time has come to completely rethink the way we are conducting phase II trials in advanced breast cancer, and consideration should be given to studies which are specifically targeted to poor prognosis patient populations, such as those resistant to anthracyclines. New drugs or strategies, active under these unfavourable circumstances, are more likely to influence favourably the course of metastatic breast cancer, and, in a second step, improve the results of adjuvant therapy for early disease.

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