Pergamon

European Journal of Cancer, Vol. 33, No. 13, pp. 2171–2182, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00262-1

Clinical Oncology Update

Review of Recent Trials of Chemotherapy for Advanced Breast Cancer: Studies Excluding Taxanes

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INTRODUCTION

A NUMBER of new agents and combinations of drug have been introduced for breast cancer over the past 2 years. The purpose of this review is to summarise all trials reported between January 1995 and December 1996.

The process of introducing new agents has become more complex recently. Not only can they be used alone or in combination at the standard dose, but the effect of increasing the dose and reducing the dose interval using haemopoeitic growth factors (HGFs), can also be assessed, as can increasing the dose even further by using peripheral blood progenitor cell (PBPC) support. The complexity of possible potential studies is outlined in Figure 1. Yet another complication of the evaluation of drugs in breast cancer is that treatment may be initiated at different stages of disease, e.g. first- or second-line chemotherapy for advanced disease or for locally advanced disease. In this review we have therefore categorised the studies as follows:

Advanced breast cancer
- (a) New combinations of established drugs
- (b) Dose intensification using HGFs
- (c) Dose intensification using PBPC

Locally advanced breast cancer
Neoadjuvant therapy
New agents

We assessed all reports of breast cancer trials on Medline, BIDS (Bath Information and Data Services) and Abstracts from the major international meetings on cancer. Abstracts were discarded when basic data required for interpretation of the trial were not obvious. Many trials are reported on more than one occasion, and only the most recent or the published paper has been used.

ADVANCED BREAST CANCER

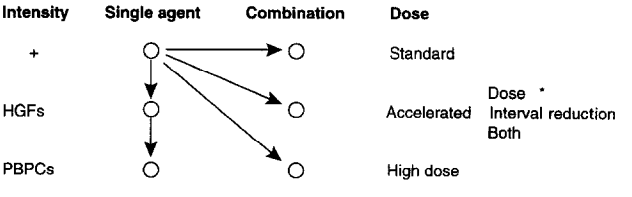
New combinations of established agents

A large number of new combinations of established agents have been reported. Some of the chemotherapy agents have been in use in the clinic for many years (e.g. platinum compounds, ifosfamide) but only used in breast cancer relatively recently. In phase II studies in patients with no previous chemotherapy for advanced disease, platinum-containing regimens (RR, response rate 37–86%) and anthracycline-containing regimens (RR 32–90%) appeared superior to combinations not containing these agents (RR 44–69%, Table 1). The response rates in randomised studies comparing two combinations of drugs are generally lower than those reported in the phase II studies alone. In some studies anthracycline-containing regimens gave higher response rates compared with non-anthracycline-containing regimens [23, 27]. Vindesine in combination appears disappointing [31].

In general, the response to second-line regimens is disappointing and no regimen looks particularly promising. Table 1(b) shows studies with apparent high response rates to second-line therapy including chemotherapy naïve as well as previously treated patients. Platinum combinations are particularly disappointing.

Dose intensification using HGFs

Most regimens used for intensification contain anthracyclines (Table 2). The highest response rates are generally all in studies where not only the dose of chemotherapy is increased, but the interval between doses reduced (so called 'dose-dense therapy') [62–64, 68]. Also high complete response (CR) rates are seen but usually (except study [63]) the duration of responses are not increased over standard therapy. Reducing the dose interval was also shown to produce a higher response rate in a randomised study [73].



*Increasing dose and reducing dose interval has been called dose dense therapy.

HGFs = Haemopoietic growth factors
PBPCs = Peripheral blood progenitor cells

Figure 1. Introduction of new chemotherapeutic agents for breast cancer. The arrows indicate the progression of clinical trials (e.g. after a single agent has been tested at a standard dose, it can then be tested in a combination regimen, either at standard or increased doses, or HGFs/PBPCs could be added to the single agent trial).

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Received 18 Apr. 1997; accepted 6 May 1997.

Dose intensifications using PBPC

A large number of phase II trials of high-dose chemotherapy (HDC) alkylating agents have been performed in women with advanced breast cancer (Table 3). These approaches are usually relatively unrewarding in women with tumours resistant to standard chemotherapy for advanced disease. This has led to the use of HDC, usually after response to standard chemotherapy for advanced disease and have made assessing the place of HDC difficult. Complete remission rates vary from 16 to 51% [86, 95]. It is difficult to determine how important these responses are because of the lack of controls and the relatively short follow-up. Although the results appear impressive, it is clear that patients are highly selected. Rahman and colleagues [96] selected patients from his database who fit the criteria for high-dose studies, i.e. young with a good performance status, to determine how well they fared with standard FAC (5-FU, DOX, CYCLO) as given at the M.D. Anderson Cancer Centre, Texas, U.S.A. Twenty-five per cent of these patients had a complete remission and 19% of them lived for 5 years—figures that are comparable with the results of HDC (Table 3).

Very recently, the first randomised trial of HDC versus standard chemotherapy for advanced disease was reported

Table 1. *New combinations of established agents for advanced breast cancer*

(a) Trials with patients who have not received previous chemotherapy

Main agent	Additions	Number of pts	Response rate (%)	Reference
Phase II				
CISPLAT	MTX VB DOX	29	83	1
CARBO	EPI 5-FU	50	86	2
	EPI 5-FU (IFN)	52	81	3
CARBO	5-FU (Inf), EPI	36	81	4
CARBO	CYCLO + 5-FU	19	37	5
DOX	5-FU VCR CYCLO (PO)	83	48	6
DOX (x4)	CYCLO MTX 5-FU (x4)	44	77	7
EPI 120	CYCLO	40	75	8
EPI	LONID IFN	40	90	9
EPI	5-FU/LV CYCLO	18	78	10
EPI (HD)	CYCLO	40	75	11
EPI	IFOS VCR (Inf)	28	32	12
EPI	IFOS	331	45	13
LIPO DOX	5-FU CYCLO	29	69	14
Pirarubicin	5-FU CYCLO	40	62	15
ETOP	CYCLO	?	58	16
5-FU/LV	MITOX	24	50	17
5-FU/LV	CYCLO MITOX	34	44	18
TEGAFUR/LV	MITOX	32	63	19
Randomised				
5-FU EPI CYCLO versus		141	43	20
5-FU, MITOX, CYCLO			30	
EPI LONID versus		207	60	21
EPI			40	
EPI versus		18	61	22
MITOX		19	21	
CYCLO MTX 5-FU versus		86	40	23
CISPLAT EPI MTX VCR/MTX CISPLAT ETOP MITO-C		81	75	
CYCLO 5-FU DOX versus		50	68	24
CYCLO 5-FU MITOX		50	68	
CYCLO DOX 5-FU versus		164	50	25
VB DOX THIO HALOTESTIN versus		164	57	
VB DOX THIO HALOTESTIN/CYCLO MTX 5-FU VCR PRED		163	51	
5-FU DOX CYCLO versus		?	54	26
5-FU (Inf) CYCLO DOX		?	53	
5-FU EPI CYCLO versus		224	58	27
CYCLO MTX 5-FU		237	44	
5-FU CYCLO EPI versus		79	44	28
5-FU CYCLO MITOX		79	30	
5-FU DOX (weekly) CYCLO versus		129	54	29
5-FU DOX CYCLO		129	53	
MITOX CYCLO TAM versus		56	33	30
DOX CYCLO TAM		69	48	
VINDESINE + EPI (Inf) versus		255	34	31
VINDESINE + MITOX		?	26	

Table 1—*contd*

(b) Trials with patients who have received previous chemotherapy

Regimen	Additions	Number of pts	Response rate (%)	Reference
Phase II				
Cisplatin	5-FU/LV IFN	34	26*	32
Cisplatin	ETOP TAM MITOX	44	41*	33
Carboplatin	IFOS	25	8	34
	5-FU CYCLO	29	28	35
Carboplatin	CYCLO 5-FU	29	28*	36
Carboplatin	DOX CYCLO	27	63*	37
DOX	5-FU (Inf) VCR CYCLO	83	48*	38
EPI	IFOS VCR (Inf)	28	32	39
EPI	IFOS	16	50	40
EPI	VCR (Inf) IFOS	28	32	41
5-FU/LV	Alone	22	25	42
	MITO-C	18	28*	43
	MITOX	26	27	44
	THIO	35	40	45
5-FU (Inf)	Alone	80	21	46
5-FU/LV	Dipyridamole MITOX	15	13	47
5-FU/LV	THIO	30	40*	48
5-FU/LV	CYCLO MITOX	34	44*	49
5-FU (Inf)	HD-LV	43	41	50
5-FU (Inf)	IFN	26	8	51
5-FU/LV	MITOX	26	27	52
TEGAFUR	LV MITOX	32	62*	53
TEGAFUR/LV	CYCLO MTX	38	47*	54
ETOP	CISPLAT	26	31*	55
MITOX	DOXIFL + MPA	16	50	56
	MTX MITO-C MGA	29	52	57
VCR	5-FU DOX CYCLO	34	48*	58

*Some previously untreated patients in study. Inf, infusion; PO, oral; MGA, megestrol acetate; IFN, interferon; DOX, doxorubicin; HD, high-dose; EPI, epirubicin; LIPO, liposomal; 5-FU, 5-fluorouracil; LV, leucovorin; CYCLO, cyclophosphamide; MITOX, mitoxantrone; LONID, lonidamine; CISPLAT, cisplatin; MTX, methotrexate; VCR, vincristine; ETOP, etoposide; MITO-C, mitomycin-C; VB, vinblastine; THIO, thiotepa; PRED, prednisolone; TAM, tamoxifen; IFN, interferon-α; IFOS, ifosfamide; MPA, medroxyprogesterone acetate; CARBO, carboplatin.

Table 2. Dose intensification using haemopoietic growth factors in advanced breast cancer

Regimen	No of patients	Response rate (%)	CR (%)	MDR (wks)	Reference
DOX 90 CYCLO q 3 wks x 6 + GM-CSF	28	83	32	8	59
DOX IFOS + G-CSF	18	83	?	?	60
EPI 110 x 6q 4 wks + G-CSF	42	38	33	31	61
EPI IFOS x 4q 2 wks + G-CSF	20	90	30	29	62
EPI 120 CYCLO 1g q 2–3 wks + G-CSF	59	87	28	72	63
EPI 120 CYCLO q 2 wks x 6–8 + G-CSF	22	86	50	44	64
EPI 120 CYCLO 600 x 4–8 + G-CSF q 3 wks	26	65	22	40	65
EPI 5-FU/LV CYCLO + G-CSF	57	72	?	?	66
EPI 130 LONID IFN q 3 wks + G-CSF	40	90	35	?	67
EPI 70 5-FU CYCLO q 2 wks x 6 + G-CSF	8	87	0	?	68
EPI 110 q 4 wks x 6 + G-CSF	42	38	4	31	69
EPI 5-FU/LV CYCLO + G-CSF	64	72	25	?	70
MITOX CYCLO + GM-CSF	?	60	20	21	71
5-FU/LV MITOX CYCLO + G-CSF	32	68	12	9	72
Randomised					
5-FU EPI 50 CYCLO 600 q 3 wks + G-CSF	20	25	5	9.2	73
versus		$P<0.05$		$P=0.08$	
5-FU EPI 50 CYCLO 600 q 2 wks + G-CSF	20	50	15	12.3	

q, every; G/GM-CSF, granulocyte/granulocyte-macrophage stimulating factor; wk, week. For other abbreviations see Table 1 legend.

[95]. 45 patients received two cycles of high-dose etoposide, mitoxantrone and cyclophosphamide with autologous bone marrow transplant (ABMT) or PBPC rescue (with no induction therapy). This was compared with six cycles of standard chemotherapy with vincristine, mitoxantrone and cyclophosphamide given to another group of 45 patients. The response rate, response duration and survival rate were approximately double in the HDC arm compared with the standard arm. This highly important study is the first to show the superiority of HDC in a randomised trial.

Table 3. High-dose chemotherapy with ABMT/PBSC support for advanced disease

Regimen	*n*	CR + PR %	Survival	Reference
Advanced disease				
BUSULPH CYCLO	21	70	25% 2-year DFS	74
CYCLO THIO CARBO	62	only pts who responded	31% 5-year PFS	75
CYCLO MITOX MELPH MTX VCR ETOP CARBO	15	100	ND	76
CYCLO CARBO	39	ND	stage II–III pt 79% 14m RFS stage IV 23% 22m RFS	77
CYCLO MITOX VB CARBO	80	86	median 33m OS	78
CARBO MITOX THIO	25	ND	80% stage IV recurred by 14 mth	79
OESTROGEN CARBO ETOP CARBO	28	ND	88% 19 mth OD	80
IFOS ETOP CARBO	34	ND	84% 2 yr OS	81
CYCLO THIO CARBO	107	mixture of pretreatment CR/PR	49% 1 yr PFR	82
THIO CARBO PHENYLALANINE	26	mixture of pretreatment CR/PR	69% 5 mth PFS for ABC	83
CYCLO CARBO ETOP	17	62	No adv for chemoresistant patients	84
CYCLO BCNU	20	ND	17 mth median	85
IFOS CARBO ITOP	44	50	Previously treated	86
Consolidation after induction of CR in advanced disease				
CYCLO ETOP THIO MITOX	29	in CR	34 mth	87
CARBO ETOP MELPH	21	in CR	80% 24 mth OS	88
Randomised trial				
CYCLO CARM CISPLAT	423	Immediate HD therapy versus delayed therapy	OS 1.9 OS 3.2 (P 0.04)	89
CARBO THIO CYCLO	110	65 (including previous CR)	Med surv 20 mth	90
Multiple courses of high-dose chemotherapy				
[CYCLO CARBO ETOP]$_2$	24	33 CR from PR	PFS 32% @ 23 mth	91
[CARBO CYCLO ETOP]$_3$	48	60	ND	92
[CYCLO THIO]—[MELPH] after induction of RR	27	88	56% 30 mth OS	93
[MITOX CYCLO VB]$_2$	29	ND	15 mth median	94
Randomised trials				
[CYCLO 2.4 g/m^2 MITOX 35–45 mg/m^2 x 2 ETOP 2.5 g/m^2] versus	45	95	Survival duration signif longer for HD-CNV	95
[CYCLO 600 mg MITOX 12 mg/m^2 x 6.8 VCR 1.4 mg/m^2]	45	51		

ABMT, autologous bone marrow transplant; BUSULPH, busulphan; MELPH, melphalan; CARM, carmustine; CR, complete response; PR, partial response; ND, not done; PFS, progression-free survival; DFS, disease-free survival; mth, months; adv, advantage. For other abbreviations see legend to Table 1.

LOCALLY ADVANCED BREAST CANCER

Locally advanced breast cancer is a useful opportunity to try new approaches to chemotherapy since objective and often pathological responses can be documented. However, one drawback is the relatively low numbers of patients who present with this type of disease. The response rate to standard chemotherapy in locally advanced disease is exemplified by a study in which 140 patients were treated with FAC [102]. Eight per cent had complete remissions and 57% had partial remissions (Table 5). Using HGFs, a higher complete response rate has been reported in some studies (36% [65] and 47% [64]), although the pathological CR rate was not reported. In studies where this was reported it ranged from 0 to 11% [107–110]. Several studies reported high-dose chemotherapy using PBPC or ABMT. Very high CR rates (55–78%) and 20–25% pathological CRs were reported [113–115]. These results are the best seen for macroscopically detected breast cancer, but conversely, in terms of pathological CRs, indicate the possible limitations of chemotherapy.

NEOADJUVANT THERAPY

Neoadjuvant therapy may be defined as treatment given with the intention of preserving the breast using limited surgery. Data are limited (Table 6), but it appears that regimes containing platinum and anthracyclines or vinorelbine and anthracyclines are associated with high complete response rates and pathological CRs. In a randomised study, a combination of CMF EPI-VCR was slightly superior to CMF [123]. Results from studies using HGFs do not appear superior to regimens containing anthracyclines and platinum compounds given without HGF support, although the data are limited. In a randomised study of cyclophosphamide, doxorubicin and fluorouracil, intensification using G-CSF in one arm resulted in a higher overall response rate but no increase in pathological CR [131].

In a randomised study where the G-CSF was used to maintain the dose intensity of FEC, the overall and complete response rates were high but not significantly different from the non-G-CSF arm [129].

Table 4. Effect of patient selection in advanced breast cancer. All patients were given FAC as first-line therapy for advanced disease. High-dose candidates are patients who meet the eligibility criteria for most high-dose trials [96]

	High-dose candidates	Non-candidates
n (%)	590 (43)	788 (57)
Median age	49 (22–60)	605 (25–82)
% RR (*n*)	91.4 (539)	47.4 (374)
% CR	25.3	8.6
Median survival (m)	28	17
3 yr survival (m)	38	21
5 yr survival (m)	19	7
10 yr survival (m)	5	2

NEW DRUGS AS SINGLE AGENTS AND IN COMBINATION

Vinorelbine (Navelbine)

This agent is a microtubule inhibitor similar to other vinca alkaloids but has greater activity. It has high single-agent activity both in chemotherapy naïve (21–44% response) and previously treated (11–64% response) patients with advanced disease (Tables 7a and Table 7b). In combination it is highly active with anthracyclines and cisplatin in chemotherapy naïve patients and has good activity with mitomycin C, mitroxantrone, ifosfamide and cisplatin (40–89% response) in previously treated patients. However, these responses do not appear to be greater than vinorelbine used alone in this clinical situation.

Topoisomerase inhibitors

These agents cause tumour cell death by inhibiting the DNA repair activity of topoisomerase. Several inhibitors are in early clinical trial. Topotecan produced a 36% response (5/14) [181, 182]. Combination studies with these important group of compounds are in progress.

Anthracyclines

Several new anthracyclines are in clinical trial, although response rates in combination with 4HTP doxorubicin or pirarubicin (Tables 1 and 8) appear to be similar to those produced by doxorubicin and epirubicin. Doxorubicin encapsulated in polyethylene glycol (PEG) coated liposomes (Caelyx) is in phase II clinical trial [183]. PEG coating of the liposome diminishes uptake in the reticulo-endothelial system and is associated with a prolonged half-life and high tumour uptake. The relative lack of toxicity (very little nausea, vomiting or hair loss) makes it an interesting agent to explore in combination.

Other drugs

Table 8 outlines various phase II studies with agents usually used in previously treated (usually multiple regimens) patients and the response rates appear rather low. However, gemcitabine, idarubicin and tomudex look promising.

SUMMARY

- Randomised trials in advanced breast cancer have shown anthracycline regimens to be slightly superior to other combinations, but no difference has been established between the type of anthracycline used in combination.
- New combinations of existing drugs, with the introduction of carboplatin, 5-fluorouracil with leucovorin, and etoposide and ifosfamide in combinations, have been associated with response rates up to 89%.
- The value of high-dose regimens has been uncertain. However, a recently reported randomised trial [95] in which two high-dose therapies were compared with standard chemotherapy has shown an approximate doubling of the response rate, response duration and survival in favour of high-dose therapy.

Table 5. Chemotherapy for locally advanced breast cancer

Regimen	No of patients	Response rate	CR (%)	% Path CR	Reference
Standard chemotherapy					
CISPLAT DOX CYCLO	30	70	?	8	97
CISPLAT DOX CYCLO	14	100	?	?	98
CISPLAT DOX CYCLO	30	77	7	8	99
CISPLAT 5-FU DOX CYCLO ETOP MITO-C	34	73	?	?	100
DOX IFOS	15	93	?	13	101
DOX CYCLO 5-FU	140	68	8	6	102
DOX CYCLO 5-FU x 2–3	22	?	?	?	103
EPI CYCLO 5-FU	66	90	20	5	104
5-FU infusion	12	73	25	7	105
CYCLO MTX 5-FU	189				106
With growth factors					
CISPLAT IFOS ETOP	10	100	20	10	107
DOX CYCLO	33	100	43	7	108
EPI CYCLO 5-FU q 2 wks	26	?	?	11	109
EPI CYCLO q 2	32	88	11	0	110
EPI CYCLO 5-FU q 2 wks	40	63	14	?	111
EPI CYCLO q 3 wks	26	80	36	?	65
EPI CYCLO q 2 wks	19	?	47	?	64
EPI CYCLO q 2 wks	32	88	9	?	112
High-dose with PBPC/ABMT					
CYCLO CARBO THIO (PBPC)	20	100	55	20	113
CYCLO DOX (PBPC)	9	100	78	25	114
CYCLO MITOX MELPH (ABMT)	40	90	60	?	115

q, every; path CR, pathological CR. See legends to Tables 1 and 3 for other abbreviations.

- Response rates in locally advanced breast cancer given intensified therapy with or without HGF/PBSC support are at or near 100%. Of importance is the 20% pathological complete remissions seen with the best regimens.
- Neoadjuvant chemotherapy such as paclitaxel and doxorubicin and epirubicin, cisplatin, and fluorouracil and intensified regimens are associated with response rates at or near 100%. A randomised trial of preoperative versus post-operative chemotherapy shows a trend towards improved PFS in the former group [121].
- Vinorelbine is highly active when used as a single agent and when incorporated into combination chemotherapy regimens. Gemcitabine, idarubicin and liposomally

Table 6. *Neoadjuvant therapy*

Regimen	No. of patients	Response rate	CR (%)	% Path CR	Reference
Standard chemotherapy					
Non-randomised					
CISPLAT DOX CYCLO 4 q 3 wks x 5	26	100	?	46*	122
CISPLAT EPI 5-FU inf q 3 wks x 8	50	98	66	20	116
CIS PLAT CYCLO DOX q 3 wks x 4	12	100	?	25	98
EPI VIN MTX q 4 wks	69	77	26	21	117
EPI CYCLO VIN	16	57	38	?	119
MITOX MTX TAM q 3 wks x 8	295	83	19	?	122
CYCLO MITOX 5-FU q 3 wks	63	62	22	?	118
Randomised					
CYCLO MTX 5-FU q 4 wks x 4	101	66	13	1	123
versus					
EPI CYCLO MTX 5-FU VCR q 4 wks x 4	98	74	20	6	
With growth factors					
Non-randomised					
CYCLO EPI 5-FU q 2 wks	36	100	?	0	124
CYCLO THIO-DOX VIN q 3 wks	40	92	49	23	125
CYCLO EPI 5-FU q 3 wks	46	?	?	13	109
DOX q 2.5 wks	34	100	?	?	126
EPI q 2–3 wks	29	87	28	?	63
5-FU EPI CYCLO q 3 wks	20	?	?	15	127
Randomised					
CYCLO DOX 5-FU q 3 wks	49	76	?	=	128
versus					
CYCLO DOX 5-FU q 2 wks + G-CSF	48	98	?	=	
CYCLO EPI 5-FU x 4 q 3 wks	59	93	37	28*	129
versus					
CYCLO EPI 5-FU x 4 q 3 wks + G-CSF	61	90	38	14*	

*Including *in situ* cancer. q, every; =, equivalent path CR; VIN, vinorelbine. See legends to Tables 1 and 3 for other abbreviations.

Table 7a. *Vinorelbine in the treatment of chemotherapy-naïve patients*

Regimen (mg)	*n*	RR	% CR	MDR	Reference
Single agent					
Oral	98	24	5	?	110
VIN 30 130 mg/m^2 weekly	63	44	8	17.9	131
Combination					
VIN 25 mg/m^2 DOX 50 mg/m^2	58	57	16	?	132
VIN 15–30 mg/m^2 MITOX 3–6 mg/m^2 q 1 wk + G-CSF	41	51	5	9.5	133
VIN 25 mg/m^2 q1 wk EPI 25 mg/m^2 q 1 wk + G-CSF 30 > mcg/d for 6 weeks	27	74	15	10	134
VIN 35 mg/m^2 (1 & 15) IFOS 2 g/m^2 (d1–3)	43	58	14	12	135
VIN 25 mg/m^2 (d1 & 8) DOX 25 mg/m^2 q 3 wks	22	82	14	?	136
VIN 25 mg/m^2 (d1 & 8) q 3 wks EPI 90 mg/m^2 d1 q 3 wks + G-CSF	25	68	12	?	137
VIN 25 mg/m^2 EPI 25q 1 wk + G	9	89	11	?	138
VIN 17.5–30 mg/m^2 IFOS mg/m^2	43	58	?	?	139
VIN 25 mg/m^2 EPI 25 mg/m^2	9	89	?	?	140
CISPLAT 25 mg/m^2 MITOX 12 mg/m^2 q 3 wks VIN 25 mg/m^2	20	75	20	?	141
IFOS 2 g/m^2 (d1–3) VIN 35 mg/m^2 (d1 + 15)q 4 wks	28	57	3	9	142
5-FU 750 mg/m^2 d1–5 inf VIN 30 mg/m^2 d1 + 5q 4 wks	57	40	?	?	143

q, every. For other abbreviations see legends to Tables 1, 3 and 6.

Table 7b. Vinorelbine in the treatment of patients who have previously been treated with chemotherapy

Regimen (mg)	*n*	RR	% CR (months)	MDR (months)	Reference
Single agent					
Oral	131	11	0	?	130
25–30 mg/m^2 q 3 wks	44	34	6	7	144
25 mg/m^2 q 1 wks	14	64	7	7	145
25 mg/m^2 q 1 wks + G-CSF 300 mcg	34	47	9	11	146
80–100 mg/m^2/week	13	46	?	?	147
Combination					
Non-randomised					
VIN 15–20 mg/m^2 CYCLO DOX MTX 5-FU/LV	9	66*	?	?	148
VIN mg/m^2 CARBO	41	46*	?	?	149
VIN 25 mg/m^2 MITOX CISPLAT	20	75*	?	?	150
VIN 30 mg/m^2 wk x 4 MITO C 8 mg/m^2 q 4–6 wks	20	35	5	5	151
CISPLAT 20 mg/m^2 VIN 6 mg/m^2 bolus 6/day inf	56	43	4	4.5	152
VIN 25 mg/m^2 5-FU 600/LV, MTX 6 mg/m^2	25	28	?	?	153
CARBO VIN	41	46	?	?	154
VIN 30 mg/m^2 THIO	32	28	6	9	155
VIN 30 mg/m^2 5-FU 750 mg/m^2	57	40	?	?	143
VIN 15–30 mg/m^2 MITOX	41	51*	?	?	156
VIN 25 mg/m^2 5-FU/LV MITOX	25	28	?	?	157
VIN 40 mg/m^2 MITO-C + G	55	73*	?	?	158
Randomised					
DOX 70 mg/m^2 versus	151	30	?	6	159
DOX 50 mg/m^2 + VIN 25 mg/m^2	151	35	?	6	
VIN 30 mg/m^2 versus	183	46 (include SD)	?	12	160
MELPH		28 (include SD)	?	8	

*Includes mixture of previously treated and untreated patients.

Table 8. Other new drugs usually used in previously treated patients

Regimen (mg)	*n*	RR (%)	Subjects	Reference
CI-973				
Platinum diamine complex	25	8	Previous CT for MBC	161
Etoposide oral	26	19	Previous CT for MBC	162
Etoposide oral	27	10	Previous CT for MBC	163
Etoposide oral	21	28	1st-line for MBC	164
Etoposide	26	19	Previous treated for MBC	165
Etoposide oral	21	10	Previous CT for MBC	166
Gemcitabine	40	25	14 pts chemo naïve 7 pts had adj CT 19 pts previous CT for MBC	167
Gemcitabine	44	25	Some previous treated pts for MBC	168
Gemcitabine	26	46	1st-line for MBC	169
Gemcitabine	9	56	1st-line for MBC	170
Gemcitabine	40	25	Some previous treated pts	171
Idarubicin	28	26	1st-line for MBC	172
Idarubicin	22	36	Some previous treated	173
Idarubicin	49	33	1st-line for MBC	174
Ifosfamide	20	15	First line	175
Liposomal doxorubicin	43	37	First line	176
Mitoxantrone	27	26	Elderly patients (≥ 68 yrs)	177
Piroxantrone	32	6	Prev treated for MBC	178
Tomudex	43	26	Hormone refractory pts 39% prior adj chemotherapy	179

MBC, metastatic breast cancer; CT, chemotherapy; adj, adjuvant.

encapsulated anthracyclines all look interesting and are awaiting further clinical investigations.

CONCLUSIONS

The introduction of active new chemotherapeutic agents and the ability to intensify treatments safely by using HGFs and PBSC transplants has led to highly active pre-operative and adjuvant therapies, which may be a significant improvement over standard treatments, with evidence of prolonged survival in advanced breast cancer. Although high response rates can be achieved in advanced breast cancer, a major problem is to maintain remission. New approaches are required.

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