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Chemotherapy in metastatic breast cancer: A summary of all randomised trials reported 2000–2007

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ABSTRACT

Aim: To summarise the findings of all randomised trials comparing chemotherapy regimens for metastatic breast cancer that were reported between 2000 and 2007 inclusive.
Methods: We searched the specialised register of clinical trials maintained by the secretariat of the Cochrane Breast Cancer Group (CBCG) from 2000 to 2007, and abstracts from the American Society of Clinical Oncology (ASCO) annual scientific meeting (2000–2007).
Results: Eighty reports of 63 trials were identified as eligible for this review. Whilst over 30% of the trials reported a statistically significant difference in response rate or progression free survival, only 8 trials (13%) reported a difference in overall survival. Thirty percent reported quality of life data. Very few trials examined the critical clinical questions of duration and the relative merits of combination *versus* sequential single agent chemotherapy.
Concluding statement: There is little evidence from trials reported from 2000 to 2007 that major survival differences exist between many commonly employed chemotherapy regimens.

1. Introduction

For women with metastatic breast cancer, the aims of treatment are to improve quality of life and to prolong survival, without realistic hope of cure. Using anti-cancer treatments to control disease-related symptoms and slow progression of disease, minimising treatment-related toxicity and reducing the intrusion of the disease and treatment on a patient's life are all important components of clinical care. Metastatic breast cancer is either initially insensitive to endocrine therapy or eventually becomes so, and cytotoxic chemotherapy thus plays an important role in the treatment of most patients.

Many hundreds of randomised trials have been conducted comparing different chemotherapy drugs, doses, combinations, durations and sequences in an attempt to improve patient outcomes. However, because of the quantity and variety of data, drawing conclusions about the best way to use chemotherapy remains difficult.

The Cochrane Breast Cancer Group has facilitated a series of meta-analyses of chemotherapy in metastatic breast cancer in an attempt to clarify the situation (Table 1).[1–6] In terms of drug classes, only taxanes have been shown to provide an overall survival advantage when compared to non-taxane-containing regimens, and this benefit is modest. Time to progression and response rate also favour taxane-containing regimens. In contrast, no overall survival advantage is seen in favour of anthracycline or platinum-containing regimens. Whilst anthracyclines can improve time to progression and response rate, they are associated with significantly more toxicity than non-anthracycline regimens. Platinums are associated with better response rates, but again at the cost of significant toxicity.

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Table 1 – Summary of Cochrane meta-analyses concerning chemotherapy in metastatic breast cancer

Trial (ref)	Overall survival		Time to progression		Response rate (higher OR= benefit for experimental arm)		Toxicity
	HR	*95% CI, p-value*	*HR*	*95% CI, p-value*	*OR*	*95% CI, p-value*	
Combination *versus* single agent (1)	0.88*	0.83–0.94, $p = 0.0001$	0.78	0.73–0.83, $p = 0.00001$	1.28	1.15–1.42, $p = 0.00001$	More toxic
Taxanes (2)	0.93*	0.86–1.00, $p = 0.05$	0.92	0.85–0.99, $p = 0.02$	1.34	1.18–1.52, $p = 0.00001$	Not more toxic
Anthracyclines (3)	0.97	0.91–1.03, $p = 0.35$	0.84	0.77–0.91, $p = ?$	1.34	1.21–1.48 $p = ?$	More toxic
Platinums (4)	1.00	0.88–1.15, $p = 0.96$	1.06	0.95–1.19, $p = 0.31$	1.47	1.23–1.76, $p = 0.0001$	More toxic
Adding drugs (5)	0.96	0.87–1.07, $p = 0.47$	0.93	0.81–1.07, $p = 0.31$	1.21	1.01–1.44, $p = 0.04$	More toxic
High-dose chemotherapy (6)	No diff.		RR 2.84 (EFS)	1.07–7.50			More toxic

*Statistically significant, no heterogeneity.
EFS – event free survival.

Other Cochrane reviews have found a modest survival advantage for combination regimens compared to single agents but with more toxicity, and that the addition of chemotherapy drug or drugs to an established regimen or the use of high-dose chemotherapy with stem-cell support does not result in better overall survival, although modest improvements in progression free survival may be seen at the cost of extra toxicity. Many of these reviews are based on old trials.

We therefore aimed to identify, review and summarise all randomised trials published between 2000 and 2007 that compared chemotherapy regimens for metastatic breast cancer and contained at least 150 patients. We did not attempt a formal meta-analysis on such a heterogeneous collection of trials. We did not examine trials of targeted therapies.

2. Methods

2.1. Criteria for selected studies

We selected randomised controlled trials comparing chemotherapy regimens used in women with metastatic breast cancer. We excluded trials testing targeted therapies. In order to exclude small, hypothesis-generating studies, we arbitrarily limited our selections to trials that had greater than or equal to 150 patients.

2.2. Search methods

The specialised register maintained by the Secretariat of the Cochrane Breast Cancer Group (CBCG) was searched. Details of the search strategy applied by the Group to create the register and the procedure used to code references are described in the Group's module on the Cochrane Library. In brief, a comprehensive search is carried out monthly, and trained coders identify and categorise trials based on predetermined criteria. The register includes both published and unpublished (including ongoing) trials identified from the searches of electronic databases including MEDLINE, EMBASE and the Cochrane Controlled Trials Register, and hand searching of journals and conference proceedings.

All references that had been assigned the CBCG codes 'advanced' and 'chemotherapy' in the specialised register were compiled, and the abstracts were screened in an attempt to determine if the reference pertained to a randomised trial in women with metastatic breast cancer comparing one chemotherapy regimen with another. The complete article was obtained for references that were definitely eligible, or where it was not possible to determine the eligibility based only on information in the abstract. ASCO abstracts from 2000 to 2007 were also searched using the same criteria for the selected studies. Both authors independently applied the selection criteria and differences were resolved by discussion (see Fig. 1).

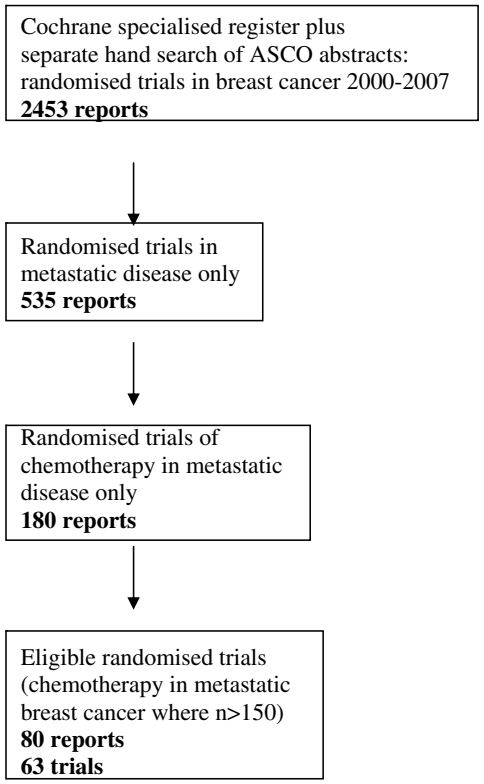

Fig. 1 – Trial selection.

Table 2 – Main characteristics of randomised controlled trials testing chemotherapy regimens reported 2000-2007

Total number of trials ($n < 150$ excluded)	63
Full publications (2000–2007)	43
Abstracts (2000–2007)	20
Trial size ($n < 150$ excluded)	
Median	305
Interquartile range	218–452
Main research questions	
Combination *versus* combination	20 trials
Combination *versus* single agent	13
Single agent *versus* single agent	3
Combination *versus* sequential single agent	3
Dose questions	
High-dose therapy	3
Dose	4
Dose intensity	2
Dose schedule	3
Drug formulation	9
Duration	3
Statistically significant benefit	
In RR	19 (30%)
In PFS	22 (35%)
In OS	8 (13%)
QOL	Measured in 19 (30%)

2.3. *Trial characteristics recorded*

Each trial was classified as to the nature of the chemotherapy comparison (combination *versus* combination, combination *versus* single agent, etc.), and number of participants. Response rates, progression free survival and overall survival data were then recorded for each arm of the trial with relevant *p*-values. Information on drug toxicity and quality of life measurements was also noted.

3. Results

There were 2453 references related to randomised trials in breast cancer dated 2000–2007 in the specialised Cochrane database, of which 535 were concerned with metastatic disease. Of these, 180 were designated as addressing chemotherapy questions and 80 reports of 63 trials were identified as eligible for this review (a comparison of chemotherapy regimens with 150 or more randomised patients). Of these, 43 have been published in the peer-reviewed literature and 20 as abstracts only to date (Table 2).

3.1. *Efficacy results*

Overall, about a third of the trial reports showed a statistically significant difference in response rate or progression free survival (30% and 35%, respectively) between arms of the trial, but only 8 trials (13% of the total) reported an overall survival benefit. Formal quality of life data were presented or mentioned in 30% of reports.

Table 3 lists the 8 trials that reported an overall survival benefit for one arm of the trial over another, in order of *p*-value. The overall survival benefits seen were of a magnitude that most observers would also deem clinically significant (unweighted median survival over 8 trials, 18.8 months *versus* 14.3 months). In 4 of these 8 trials, a combination regimen was compared with a single agent, and we might expect modest benefits in response rates, progression free survival and overall survival in this setting,[1] although one single agent regimen, capecitabine, was in fact superior to a combination, CMF. A critical unanswered question for the clinician and patient is whether the same survival benefit might be seen when the agents in a polychemotherapy regimen are administered sequentially, perhaps reducing toxicity.

Tables 4 and 5 list the 10 trials with the highest statistically significant difference between arms for response rate and progression free survival, respectively, as measured by *p*-value. As expected, there is considerable overlap. Of note, 4 of

Table 3 – Trials with an overall survival benefit (OS, months) ($p < 0.05$); superiority by p-value

Author	Number of patients (n)	Arm A	Arm B	OS A	OS B	*p*-Value	Toxicity/QOL
Feher, O	410	Epirubicin	Gemcitabine	19.1	11.8	0.0004	Toxicity similar
O'Shaughnessy	511	Docetaxel/capecitabine	Docetaxel	14.5	11.5	0.0126	Arm A more toxic but trend to less decrease in QOL. Cost effective
Jassem, J	267	Doxorubicin/paclitaxel	FAC	23.3	18.3	0.013	Arm A neutropaenia. Arm B emesis
Albain, KS	529	Paclitaxel/gemcitabine	Paclitaxel	18.5	15.8	0.018	Arm A more toxic
Bontenbal, M	216	Docetaxel/doxorubicin	FAC	22.6	16.2	0.019	Arm A more FN
Stockler, M	325	Intermittent or continuous capecitabine	CMF	22.0	18.0	0.02	Capecitabine HFS. CMF FN
Jones, S	449	Docetaxel	Paclitaxel	15.4	12.7	0.03	Docetaxel more toxic. QOL same
Icli, F	201	Oral etoposide/cisplatin	Paclitaxel	14.0	9.5	0.039	Toxicity similar

FAC – 5 fluorouracil/doxorubicin/cyclophophamide.
CMF – cyclophosphamide/methotrexate/5-fluorouracil.
GI – gastrointestinal.
HFS – hand foot syndrome.
FN – febrile neutropaenia.

Table 4 – Response Rate (RR,%) – top 10 superiority by p-value

Author	n	Arm A	Arm B	RR A	RR B	p-Value
Vahdat, L	752	Capecitabine plus ixabepilone	Capecitabine	35	14	<0.0001
Guan, Z	210	Nab-paclitaxel	Paclitaxel	52	27	<0.001
Feher, O	410	Epirubicin	Gemcitabine	40	16	<0.001
Gradishar, W	454	Nano-paclitaxel	Paclitaxel	33	19	0.001
Verrill, MW	569	Weekly paclitaxel	3 weekly paclitaxel	42	27	0.002
Bontebal, M	216	Docetaxel/doxorubicin	FAC	58	37	0.003
Paridaens, R	331	Doxorubicin	Paclitaxel	41	25	0.003
O'Shaughnessy, J	511	Docetaxel/capecitabine	Docetaxel	42	30	0.006
Harvey, V	527	Docetaxel 100 mg/m^2	Docetaxel 75 mg/m^2; docetaxel 60mg/m^2	36	23; 22	0.007
Nabholtz, J	429	Docetaxel/doxorubicin	Doxorubicin/cyclophosphamide	59	47	0.009

Table 5 – Progression Free Survival (PFS, months) – top 10 superiority by p-value

Author	n	Arm A	Arm B	PFS A	PFS B	p-Value
Alba, E	154	Liposomal doxorubicin	Nil	16.0	10.0	0.0001
Feher, O	410	Epirubicin	Gemcitabine	6.1	3.4	0.0001
O'Shaughnessy, J	511	Docetaxel/capecitabine	Docetaxel	6.1	4.2	0.0001
Vahdat, LT	752	Capecitabine plus ixabepilone	Capecitabine	5.8	4.2	0.0003
Seidman, AD	585	Weekly paclitaxel	3 weekly paclitaxel	9.0	5.0	0.0008
Paridaens, R	331	Doxorubicin	Paclitaxel	7.5	3.9	0.001
Jones, S	449	Docetaxel	Paclitaxel	5.7	3.6	0.001
Martin, M	252	Vinorelbine/gemcitabine	Gemcitabine	6.0	4.0	0.0028
Icli, F	201	Oral etoposide/cisplatin	Paclitaxel	5.5	3.9	0.003
Bontenbal, M	216	Docetaxel/doxorubicin	FAC	8.0	6.6	0.004

the 10 trials with highly significant response rate differences are comparisons of different formulations, doses or schedules of the same drug, suggesting that there is still something to learn about how we use established drugs, even as we begin to assess new ones. Of those trials that reported the greatest statistical difference in progression free survival, 4 of the 10 compared a combination regimen with a single agent. A list of all the trials, sorted by category of trial question, is shown in Table 6.

3.2. *Abstracts versus full publications*

Although one might expect a distinction between the number of positive findings in the abstracts as opposed to full manuscripts (positive findings in the abstracts being rushed into press, thus contributing to publication bias), there was no strong evidence of this. Whilst more full manuscripts reported statistically significant differences in the progression free survival (51%) than did abstracts (24%), there were no differences in the proportion of trial reports with significant response rate or overall survival differences (data not shown). Quality of life data were reported slightly more frequently in full manuscripts (32%) than in abstracts (19%), perhaps reflecting the greater time and writing space constraints on the latter.

4. Discussion

Whilst active and safe doses and combinations of drugs can be reasonably well established in small phase 2 studies, establishing the relative merits of such regimens requires larger randomised studies. Yet there is little evidence from trials reported from 2000 to 2007 that major differences exist between many commonly employed chemotherapy regimens. Meanwhile, major uncertainty exists about the appropriate duration of therapy in what is an incurable disease and about the relative merits of using a number of cytotoxics together in multi-agent regimens compared with employing single agents sequentially.

However, few studies examined these two important clinical questions (Tables 2 and 6). Three trials (Alba 10, Gennari 27, Nooij 53) compared a longer duration with a shorter duration of chemotherapy and did not find survival differences. A meta-analysis of this important question (including a number of earlier trials) is currently being conducted.[7]

Additionally, whilst we classified 13 trials as being 'combination *versus* single agent' trials, only 3 trials specifically compared a combination regimen with the sequential use of the component agents (Conte 21, Sledge 61, Soto 62). Overall survival differences were not seen. The design of both the Sledge and Soto studies conformed to a standard of clinical practice – that is, patients in the sequential arm were treated with a single agent until progression or drug-specific toxicity, then switched to the alternative agent if fit for further chemotherapy. The Conte trial design differed in that patients in the sequential arm were treated for a fixed four cycles then switched to the alternative single agent for another fixed four cycles.

Whilst most of the focus of randomised clinical trials in advanced disease is on the conventional endpoints of tumour response, progression free and overall survival, one of the major motivations for treating our patients with chemotherapy is to improve (or prevent decline in) quality of life. Yet, only 30% (19/63) of the randomised controlled trials reviewed

Table 6 – Summary of randomised controlled trials 2000–2007, comparing chemotherapy regimens in metastatic breast cancer

Author	A/P	Chemotherapy			n	Categories	RR	PFS	OS	QOL
		A	B	C			p value	p value	p value	
Pacini, P	P	FEC	EM	+/- LND	326	combo versus combo		0.01	x	N
Fountzilas	P	DD epi then pac	epi/pac		183	combo versus combo	0.1	0.27	0.17	N
Jassem, J	P	dox/pac	FAC		267	combo versus combo	0.032	0.034	0.013	N
Ackland, S	A	CEF	CMF (IV)		460	combo versus combo	0.01	0.0064	0.23	N
Namer, M	P	FAC or FEC	mitox/vin		281	combo versus combo	0.014	0.79	0.27	N
Koroleva, I	P	doc 60/dox 60	doc then dox	doc 75/50	193	combo versus combo	x	x	x	N
Luck, H	P	epi/pac	epi/cyclo		560	combo versus combo	x	0.089	x	N
Biganzoli, L	P	dox/pac	dox/cyclo		275	combo versus combo	0.51	0.65	0.49	Y
Nabholtz, J	P	doc/dox	dox/cyclo		429	combo versus combo	0.009	0.014	NS	Y
Conte, P	P	epi/pac	epi then pac		202	combo versus combo	0.023	NS	NS	Y
Fountzilas	P	epi/pac	pac/carbo		327	combo versus combo	0.32	0.04	0.25	Y
Bontenbal, M	P	doc/dox	FAC		216	combo versus combo	0.003	0.004	0.019	N
Levy, C	P	gem/doc	cape/doc		153	combo versus combo	x	x	x	N
Langley, R	P	epi/pac	epi/cyclo		705	combo versus combo	0.015	0.41	0.8	N
von Minckwitz, G	P	BMF	CMF		364	combo versus combo	x	0.0071	x	Y
Leonard, RC	A	doc/dox	doc/epi		225	combo versus combo	0.71	x	x	N
Mackey, JR	A	TAC	FAC		484	combo versus combo	x	same	x	N
Blohmer, J	A	epi/doc	epi/cyclo		182	combo versus combo	0.11	x	x	N
Chan, S	A	doc/cape	doc/gem		305	combo versus combo	0.9	0.2	x	Y
Lueck, H	A	cape/pac	epi/pac		340	combo versus combo	x	x	NS	N
Paridaens, R	P	dox	pac		331	single versus single	0.003	p<0.001	p=0.38	Y
Jones, S	P	doc	pac		449	single versus single	0.1	<0.001	0.03	Y
Feher, O	P	epi	gem		410	single versus single	<0.001	0.0001	0.0004	N
Takayama, T	P	oral FU/cyclo	oral cyclo	oral FU	181	combo versus single	0.019	0.014	0.6808	N
Nielsen, D	P	epi/cis	epi		155	combo versus single	NS	0.045	0.41	N
Berruti, A	P	LND arm	non-LND arm		371	combo versus single	0.08	0.47	x	N
Heidemann, E	P	FEC	mitox		260	combo versus single	NS	0.2	0.7	Y
O'Shaughnessy, J	P	doc/cape	doc		511	combo versus single	0.006	0.0001	0.0126	Y
Ejlertsen, B	P	epi/vin	epi		387	combo versus single	0.15	0.019	0.5	N
Zielinski, C	P	GET	FEC	FEC 90	259	combo versus single	0.093	0.557	x	N
Icli, F	P	oral etop/cis	pac		201	combo versus single	0.038	0.003	0.039	N
Reyno, L	A	dox	dox + DPPE		305	combo versus single	study closed	x	x	N
Albain, KS	A	pac/gem	pac		529	combo versus single	x	x	0.018	Y
Martin, M	P	vin/gem	vin		252	combo versus single	0.093	0.0028	0.8046	N
Vahdat, LT	A	cape + ixab	cape		752	combo versus single	<0.0001	0.0003	x	N
Katsumata, N	A	doc	doc/cyclo-doc	dox/cyclo	441	combo versus single	x	NS	NS	N
Sledge, G	P	dox/pac	dox	pac	739	combo versus sequential	BC 0.007;AC 0.004	AB 0.003;AC 0.009	NS	Y
Soto, C	A	cape/doc	cape/pac	cape->taxane	368	combo versus sequential	x	x	x	N
Conte, PF	P	epi/pac	epi->pac		202	combo versus sequential	NS	NS	NS	Y
Crump, M	A	HDC	ST		219	HDT				N
Stadtmauer	P	CMF	HDCSCT		553	HDT			x	Y
Kroger, N	P	HDT tandem	HDT single		187	HDT	0.48	0.06	0.4	N
Anon. 2000	P	FEC 100/50	FEC 75	FEC 100 rpt	417	dose	0.06	x	0.49	N
Winer, E	P	pac 250	pac 210	pac 175	474	dose	NS	0.05	0.3	Y
Harvey, V	P	doc 100	doc 75	doc 60	527	dose	0.007	0.014	0.17	N
Khoo, K	P	gem/doc	gem/pac100	gem/pac175	210	dose	x	x	x	N
Sikov, W	A	pac 150	pac 175	pac 80	244	dose intensity	NS	NS	NS	N
Ackland, S	A	epi/cyclo	epi/cyclo intense		235	dose intensity	0.3	x	x	Y
Verrill, MW	A	weekly pac	3 weekly pac		569	dose schedule	0.002	0.06	x	N
Stockler, M	A	inter cape (IC)	cont cape (CC)	CMF	325	dose schedule	0.8	0.2	0.02	Y
Seidman, AD	A	weekly pac	3 weekly pac		585	dose schedule	0.017	0.0008	0.17	N
Batist, G	P	lipo dox/cyclo	dox/cyclo		297	drug formulation	NS			N
Harris, L	P	lipo dox	dox		224	drug formulation	x	x	0.09	N
O'Brien, M	P	lipo dox	dox		509	drug formulation	x	NS	NS	N
Keller, A	P	lipo dox	vin	MMC/vinbl	301	drug formulation	x	0.11	0.71	N
Chan, S	P	lipo doc/cyclo	epi/cyclo		160	drug formulation	0.42	0.02	0.504	N
Wigler, N	A	lipo dox	dox		509	drug formulation				N
Gradishar, W	P	nano pac	pac		454	drug formulation	0.001	0.006		N
Gradishar, W*	A	nab-pac w150	nab-pac w100	doc 3w100	302	drug formulation	D vs A or B <0.001	x	x	N
Guan, Z	A	nab-pac	pac		210	drug formulation	<0.001	0.03	x	N
Gennari, A	P	pac maintenance	nil		255	duration	x	0.817	0.547	Y
Alba, E	P	lipo dox	nil		154	duration	x	0.0001		N
Nooij, M	P	CMF-stop	CMF-cont.		204	duration	x	0.011	0.77	Y

x- no data available

*arm D= nab-pac 3w/300

A= abstract, P= published, combo= combination, single= single agent chemotherapy, HDT= high dose chemotherapy with stem cell support.

Trials showing a statistically significant overall survival benefit.

reported formal quality of life measures in their abstracts. A number of factors make collecting and analysing quality of life data difficult, especially during the treatment of metastatic disease but clearly we need to know more about the subjective effects of currently used chemotherapy regimens on our patients.

We have conducted a broad overview of chemotherapy trials in metastatic breast cancer. All peer-reviewed publications as well as ASCO abstracts have been identified up to the end of 2007, but some presentations from other meetings may have been missed. We excluded trials of targeted treatment, which may in time change how we use chemotherapy in women with metastatic breast cancer. A meta-analysis was not feasible because of the variation between clinical trials and the missing data in many trials. Also, our aim was to provide a more descriptive, practical summary of the most recent clinical trials to help guide medical oncologists in their current clinical practice and also raise future important research questions.

This summary of randomised controlled trials of chemotherapy for metastatic breast cancer between 2000 and 2007 helps clarify where future research efforts should be directed. We believe there are three main areas of need: (1) the optimal duration of chemotherapy, (2) the merits of sequential single agent chemotherapy compared to polychemotherapy

regimens and (3) the need to routinely report quality of life using standardised methodology. The ultimate goals in the management of women with metastatic breast cancer need always to be borne in mind when future clinical trials are designed.

Conflict of interest statement

None declared.

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