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Combination versus sequential single-agent therapy for the treatment of metastatic breast cancer

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Abstract

The administration of combination versus single-agent chemotherapy for the treatment of metastatic breast cancer remains an unresolved and controversial issue. Previous randomised trials have shown that, while combinations offer higher objective response rates, they have not always improved time to progression, quality of life or overall survival. Rationally designed combination regimens incorporating new cytotoxic and biological agents have resulted in improved survival rates compared with monotherapy and only modest increases in toxicities. However, trials analysing combination therapies lack formal cross-over arms and do not allow comparison of these regimens with sequentially administered single-agent therapy. This paper presents the latest randomised data and reviews the advantages and disadvantages of these two approaches to the treatment of metastatic breast cancer.

Keywords: Combination chemotherapy; Single agents; Breast cancer

1. Introduction

The optimal treatment approach for metastatic breast cancer is unknown. Given the heterogeneity of this disease, with various presentations, symptoms, sites of involvement and rates of progression, it is unlikely that one single approach will be appropriate for all patients. Moreover, with an expanding list of active agents including new cytotoxics, hormone modulators and targeted biological agents, management strategies are diverse and strongly debated. At the centre of this controversy is the decision to treat patients with combinations of drugs or to administer single agents sequentially. In metastatic disease, where treatments are not curative, these decisions are dependent on many factors including patient characteristics, the nature of the disease and the choice of therapies available. Ultimately, the answer lies in providing the most effective treatment with the least toxicity. This review examines the advantages and disadvantages of combination versus sequential single-agent therapy for the treatment of metastatic breast cancer.

2. Combination or single-agent therapy?

The success of combination chemotherapy in the treatment of other malignancies such as lymphoma and germ-cell tumours has prompted the evaluation of combination therapy in breast cancer. In the adjuvant setting, poly-chemotherapy regimens offer a significant survival advantage over single-agent treatment. A meta-analysis presented by the Early Breast Cancer Trialists Collaborative Group, recently updated to include 15 years of long-term follow-up, showed that the administration of adjuvant combination

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chemotherapy is associated with a 23% reduction in the risk of recurrence and a 17% reduction in the risk of death compared with no adjuvant therapy [1]. By indirect comparison, the age-standardised effects of polychemotherapy are superior to those of single-agent therapy, for both breast cancer recurrence and mortality. Thus, combination chemotherapy is the standard treatment for early stage breast cancer.

In contrast to adjuvant treatment, systemic therapy for metastatic breast cancer is not curative. Given its palliative nature, the benefits of treatment in this setting must be weighed carefully against the associated toxicities. Since systemic therapies only have a modest impact on prolonging survival for these patients – an estimated average of 7–10 months based on comparisons with historical survival data – tolerability and quality of life (QoL) issues are important considerations in guiding treatment choices [2]. As such, combination chemotherapy using moderately active agents in this setting has not always proven to be an advantageous strategy.

3. Trials comparing combination with single-agent therapy

A number of randomised trials performed in the 1990s demonstrated that combinations, while offering increased response rates, do not always result in prolongation of survival (Table 1). Moreover, the concurrent use of multiple agents may increase the overall toxicity and can have a negative impact on patient QoL.

3.1. 5-Fluorouracil plus epirubicin plus cyclophosphamide versus single-agent mitoxantrone

In a randomised trial of 260 women with previously untreated metastatic breast cancer, patients were given a combination of 5-fluorouracil (500 mg/m^2), epirubicin (50 mg/m^2) and cyclophosphamide (500 mg/m^2) (FEC) or single-agent mitoxantrone (12 mg/m^2) every 3 weeks [3]. No significant difference was found between mitoxantrone and FEC in terms of overall response rate (ORR; 25% vs 36%; P = NS); median time to response (87 days vs 103 days; P = 0.6), median duration of response (225 days vs 182 days, P = 0.3), median time to progression (TTP; 4.4 months vs 6.2 months; P = 0.2) or median overall survival (OS; 14.1 months vs 15.8 months; P = 0.7). However, using a modified Brunner's score to judge QoL and 'gains from treatment', there was more improvement in the single-agent mitoxantrone treatment arm. This is, in part, attributable to the favourable toxicity profile of the monotherapy arm where significant differences were seen for nausea, vomiting and alopecia in favour of mitoxantrone.

3.2. Doxorubicin plus vinorelbine versus single-agent doxorubicin

The National Cancer Institute of Canada conducted a Phase III trial randomising 303 patients with metastatic breast cancer to receive either doxorubicin plus vinorelbine or doxorubicin alone [4]. All patients were vinca alkaloid- and anthracycline-na ve, and had had a maximum

Table 1
Trials comparing combination with sequential single-agent chemotherapy

Reference	Number of patients	Treatment	RR (%)	TTP (months)	OS (months)	P value
Nabholtz (1999) [9]	392	Mitomycin plus vinblastine	12	11.0[a]	8.7	0.0097
		Docetaxel	30	19.0	11.4	
Bishop (1999) [10]	209	CMFP	35	6.4	13.9	0.025[b]
		Paclitaxel	29	5.3	17.3	
Norris (2000) [4]	303	Doxorubicin plus vinorelbine	38	6.2	13.8	0.4
		Doxorubicin	30	6.1	14.4	
Nielsen (2000) [6]	155	Epirubicin plus cisplatin	66	15.3	21.5	0.4
		Epirubicin	61	8.4	15.1	
Heidemann (2002) [3]	260	FEC	36	6.2	15.8	0.7
		Mitoxantrone	25	4.4	14.1	
Berutti (2002)[c] [7]	185	Epirubicin plus cisplatin	61	10.9	28.8	NS
		Epirubicin	56	9.4	29.5	
O'Shaughnessy (2002) [11]	511	Docetaxel plus capecitabine	42	6.1	14.5	0.0126
		Docetaxel	30	4.2	11.5	
Ejlertsen (2004) [5]	387	Epirubicin plus vinorelbine	50	10.1	19.1	0.5
		Vinorelbine	42	8.2	18.0	
Albain (2004) [13]	529	Paclitaxel plus gemcitabine	40.8	5.2	18.5	0.018
		Paclitaxel	22.1	2.9	15.8	

CMFP: cyclophosphamide, methotrexate, fluorouracil and prednisone; FEC: fluorouracil, epirubicin and cyclophosphamide; NS: not significant; RR: response rate; TTP: time to progression; OS: overall survival.

[a] Results in weeks.

[b] Adjusted for prognostic factors.

[c] Both arms included lonidamine.

of one line of previous chemotherapy for metastatic disease. An efficacy analysis of 298 patients found no significant difference between the doxorubicin plus vinorelbine or doxorubicin arms for ORR (38% vs 30%; $P = 0.2$), median duration of response (7.2 months vs 6.8 months; $P = 0.6$), TTP (6.2 months vs 6.1 months; $P = 0.5$) or OS (13.8 months vs 14.4 months; $P = 0.4$), respectively. There was no significant difference between the arms in mean QoL scores over the first six cycles of therapy. However, toxicity was more pronounced in the combination arm, with a significantly higher incidence of local venous reactions (46% vs 15%), febrile neutropenia (15% vs 10%), constipation (47% vs 20%) and grade 3/4 acute neurotoxicity (6% vs 1%; $P = 0.03$). Of the patients treated in the combination arm, 11% stopped protocol treatment because of toxicity compared with 4% in the single-agent arm. In addition, more patients refused further protocol therapy in the combination arm (8% vs 2%).

3.3. Epirubicin plus vinorelbine or epirubicin plus cisplatin versus single-agent epirubicin

A trial comparing epirubicin plus vinorelbine with singe-agent epirubicin has been reported [5]. Given its comparable antitumour activity and more favourable toxicity profile, epirubicin was chosen to replace doxorubicin in this study. Three hundred and eighty-seven patients with no prior therapy for metastatic breast cancer were randomised to receive either epirubicin at 90 mg/m^2 on day 1 and vinorelbine at 25 mg/m^2 on days 1 and 8, or epirubicin alone at 90 mg/m^2 on day 1, each on a 21-day cycle. Although the median progression-free survival was significantly superior in the combination arm (10.1 months vs 8.2 months; $P = 0.019$), the median OS for the two arms was similar (19.1 months vs 18.0 months; $P = 0.50$). In addition, the incidence of grade 3/4 leucopenia, thrombocytopenia, anaemia, infection (with and without leucopenia), stomatitis and peripheral neuropathy was significantly more frequent in the combination arm. Similarly, two randomised trials comparing epirubicin plus cisplatin with single-agent epirubicin as first-line therapy for metastatic breast cancer found that the combination did not demonstrate an improvement in OS and was associated with greater toxicity [6,7].

3.4. Other trials

Although a meta-analysis of randomised trials published between 1975 and 1991 revealed a marginal survival benefit for combination versus single-agent chemotherapy, the total number of patients in the meta-analysis was small ($N = 1,986$), as were the individual trials (median number of patients <150) [8]. Furthermore, most of the trials featured older chemotherapy drugs and regimens prior to the routine use of taxanes. In recent randomised trials, single-agent docetaxel outperformed the combination of mitomycin plus vinblastine in terms of superior response rate (30% vs 12%, $P < 0.0001$), TTP (19 weeks vs 11 weeks; $P = 0.001$), and OS (11.4 months vs 8.7 months: $P = 0.0097$) [9]. Similarly, single-agent paclitaxel offered improved OS (17.3 months vs 13.9 months; adjusted $P = 0.025$) compared with cyclophosphamide plus methotrexate plus fluorouracil plus prednisone with significantly less myelosuppression, fewer infections and comparable QoL [10].

4. Rationally designed trials

The failure of combinations to significantly improve clinical survival outcomes compared with single agents in early studies has been attributed, in part, to the lack of rationally designed regimens. Ideally, combinations should comprise single agents with strong antitumour activity and no cross-resistance, with preclinical evidence of synergy and non-overlapping toxicities. This understanding has heralded a new generation of clinical trials testing rationally designed polytherapies.

4.1. Docetaxel plus capecitabine versus single-agent docetaxel

In an international Phase III trial, 511 patients with anthracycline-pretreated metastatic breast cancer were randomised to receive docetaxel (75 mg/m^2 on day 1) and capecitabine (1,250 mg/m^2 twice daily on days 1–14) or docetaxel alone (100 mg/m^2 on day 1) every 21 days [11]. Both agents have significant single-agent antitumour activity as well as distinct mechanisms of action and non-overlapping toxicities. Additionally, preclinical studies in human cancer xenograft models showed that the administration of docetaxel upregulates thymidine phosphorylase in tumour tissues. This enzyme is required for the metabolism of capecitabine to its active component within cancer cells, and, therefore, the combination shows synergistic antitumour activity [12]. As proof of concept, the objective response rate (42% vs 30%; $P = 0.006$), TTP (6.1 months vs 4.2 months; $P = 0.0001$) and OS (14.5 months vs 11.5 months; $P = 0.0126$) were significantly superior for the docetaxel plus capecitabine arm. Moreover, the gains in efficacy were achieved without compromising QoL. The side-effect profiles for the two arms were distinct with more asthenia, gastrointestinal toxicity and hand-and-foot syndrome seen in the combination arm, while more myalgias, arthralgias and neutropenic fever/sepsis were observed in the docetaxel arm.

4.2. Paclitaxel plus gemcitabine versus single-agent paclitaxel

A trial comparing paclitaxel plus gemcitabine with single-agent paclitaxel has also reported advantages for the combination arm [13]. Again, preclinical data showing synergy, as well as significant activity as single agents,

novel mechanisms of action, largely non-overlapping toxicities and established Phase II efficacy and safety data have prompted further investigation of the combination in a Phase III trial [14–16].

Five hundred and twenty-nine patients with metastatic breast cancer, previously treated with anthracyclines in the adjuvant or neoadjuvant setting, were randomised to first-line treatment with either paclitaxel (175 mg/m^2 on day 1) plus gemcitabine (1,250 mg/m^2 on days 1 and 8) or paclitaxel alone (175 mg/m^2 on day 1) every 3 weeks. The ORR (39% vs 26%; $P = 0.0007$), TTP (5.4 months vs 3.5 months; $P = 0.0013$) and median OS (18.5 months vs 15.8 months; $P = 0.018$) significantly favoured the combination arm. In spite of modestly more frequent grade 3/4 haematological and non-haematological toxicities, the gemcitabine plus paclitaxel arm was associated with a better global QoL rating [17].

4.3. Chemotherapy plus trastuzumab

Benefits similar to those obtained with combinations of docetaxel plus capecitabine and paclitaxel plus gemcitabine have been observed when chemotherapy is combined with biological agents (Table 2). A landmark trial of chemotherapy versus chemotherapy plus trastuzumab, a monoclonal antibody targeting the HER2 oncoprotein, revealed a survival advantage in favour of the combination arm [18]. In this trial of first-line therapy for HER2-overexpressing metastatic breast cancer, anthracycline-na ve patients were treated with doxorubicin plus cyclophosphamide ± trastuzumab, while anthracycline-pretreated patients received paclitaxel ± trastuzumab. In the paclitaxel ± trastuzumab arm, the addition of trastuzumab resulted in a 25% increase in median survival compared with paclitaxel alone with no increase in toxicity. This was consistent with preclinical testing of the combination, which revealed synergy for the two agents with non-overlapping side-effect profiles and distinct mechanisms of action [19]. Similar results were obtained with the combination of docetaxel plus trastuzumab versus docetaxel alone for metastatic breast cancer based on fulfilment of the same criteria [20]. Unfortunately, the addition of trastuzumab to doxorubicin plus cyclophosphamide resulted in excessive cardiac toxicity and therefore this combination is not approved for routine clinical use.

4.4. Chemotherapy plus bevacizumab

Another biological agent that has demonstrated efficacy in the treatment of breast cancer is the vascular endothelial growth factor inhibitor bevacizumab. Miller *et al.* presented the results from a large randomised trial ($N = 715$) of bevacizumab plus paclitaxel compared with single-agent paclitaxel for the first-line therapy of patients with metastatic breast cancer (ASCO meeting, Orlando, Florida, 2005; unpublished). The ORR (28% vs 14%; $P < 0.0001$), progression-free survival (11 months vs 6 months; $P < 0.001$) and median OS (hazard ratio [HR] 0.674; $P = 0.01$) all favoured the combination arm. Although there was modestly more grade 3/4 hypertension (13.3% vs 0%; $P < 0.0001$), proteinuria (2.4% vs 0%; $P = 0.0004$) and neuropathy (20.5% vs 14.2%; $P = 0.01$) in the combination arm, these toxicities were manageable.

5. The future of combination chemotherapy

It is clear from recent trials in metastatic breast cancer that combination therapy can improve ORR and often TTP compared with monotherapy. However, lacking a formal cross-over design, the question of whether these combinations can produce superior results compared with sequential single-agent therapy cannot be determined. In the study comparing docetaxel plus capecitabine and single-agent docetaxel, only 25% of patients receiving single-agent docetaxel went on to receive subsequent capecitabine chemotherapy [21]. Furthermore, a post-study analysis of this subgroup of patients revealed that those patients receiving sequential docetaxel and capecitabine had a longer median OS compared with those patients receiving the combination treatment up front [21]. Conversely, subset analyses of the trastuzumab trials showed that concurrent treatment is better than sequential single-agent use for chemotherapy plus trastuzumab in HER2-positive patients [18,20].

Table 2
Trials comparing combination chemotherapy and biological agents with chemotherapy alone

Reference	Number of patients	Treatment	RR (%)	TTP (months)	OS (months)	P value
Slamon (2001) [18]	469	Chemotherapy [a] plus trastuzumab	50	7.4	25.1	0.01
		Chemotherapy	32	4.6	20.3	
Miller (2005) [unpublished data, ASCO 2005]	715	Paclitaxel plus bevacizumab	28	11.0	NA	0.01
		Paclitaxel	14	6.1	NA	
Marty (2005) [20]	186	Docetaxel plus trastuzumab	61	11.7	31.2	
		(for survival) vs docetaxel	34	6.1	22.7	0.0325

RR: response rate; TTP: time to progression; OS: overall survival; NA: Not available.
[a] Chemotherapy in this trial was either the combination of doxorubicin plus cyclophosphamide or paclitaxel.

6. Combination versus single-agent therapy in the first- and second-line settings

Only a few studies have prospectively addressed the issue of combination versus sequential single-agent therapy for metastatic breast cancer (Table 3). Joensuu *et al.* conducted a randomised trial of first- and second-line therapy for metastatic breast cancer (Fig. 1). The trial randomised 303 patients to receive combination therapy (FEC) three times per week followed by mitomycin C plus vinblastine [MV] (at progression and then every 4 weeks) or sequential single-agent treatment (weekly epirubicin until progression, followed by single-agent mitomycin C every 4 weeks) [22]. For first- and second-line therapy, the response rates were 55% vs 48% (P = 0.21) in patients treated with FEC compared with epirubicin and 7% vs 16% (P = 0.12) in patients treated with MV versus vinblastine, respectively. There was no significant difference in TTP (10 months vs 8 months; P = 0.19) or OS (18 months vs 16 months; P = 0.62) for the two groups. Treatment-related toxicity was less frequent in the sequential single-agent arm; the prospective QoL analysis also favoured this approach.

Sledge *et al.* also conducted a large randomised trial comparing combination chemotherapy with paclitaxel plus doxorubicin versus sequential therapy with doxorubicin followed by paclitaxel or paclitaxel followed by doxorubicin for first- and second-line therapy of metastatic breast cancer [23]. Seven hundred and thirty-nine patients were entered in this trial making it one of the largest to test this hypothesis prospectively. While the combination arm offered a superior ORR and time to treatment failure compared with the sequential single-agent therapy arms, it did not improve OS or QoL. Additionally, this trial showed that doxorubicin and paclitaxel, in the doses administered, had equivalent activity; the sequence of delivery of the two agents had no impact on clinical outcome.

7. Conclusion

Recent rationally designed trials of combination therapy, incorporating newer cytotoxic drugs and biological agents, have demonstrated modestly prolonged OS without excessive toxicity and thus support a role for combination therapy in the treatment of patients with advanced breast cancer. This is perhaps most evident when adding chemotherapy to biologically targeted treatment as the data suggest that concurrent therapy may be optimal. While promising, it is yet to be determined whether chemotherapy combinations offer a superior clinical outcome compared with sequentially administered single-agent therapy, which has previously proven to be a feasible strategy in this palliative setting. Given the heterogeneous nature of metastatic breast cancer, it is unlikely that a single approach to management will be appropriate for all patients. In the case of frail or elderly patients with significant comorbidities, where the toxicities of treatment may outweigh any potential benefits, sequentially administered single agents may be a preferred option. Younger patients without comorbidities and large burdens of visceral or symptomatic involvement could be more appropriately treated with combinations, where there are higher response rates and shorter times to response.

Table 3
Rationally designed trials comparing combination chemotherapy with sequential single-agent therapy

Reference	Number of patients	Treatment	RR (%)	TTP (months)	OS (months)	P value
Joensuu (1998) [22]	303	FEC → MV	55 → 7	10.0	18.0	0.62
		E → M	48 → 16	8.0	16.0	
Sledge (2003) [23]	739	Doxorubicin/paclitaxel	47	8.0[a]	22.0	0.77
		Doxorubicin → paclitaxel	36	5.8[a]	18.9	
		Paclitaxel → doxorubicin	34	6.0[a]	22.1	

RR: response rate; TTP: time to progression; OS: overall survival; FEC: 5-fluorouracil/epirubicin/cyclophosphamide; M: mitomycin C; V: vinblastine; E: epirubicin.
[a] Time to treatment failure.

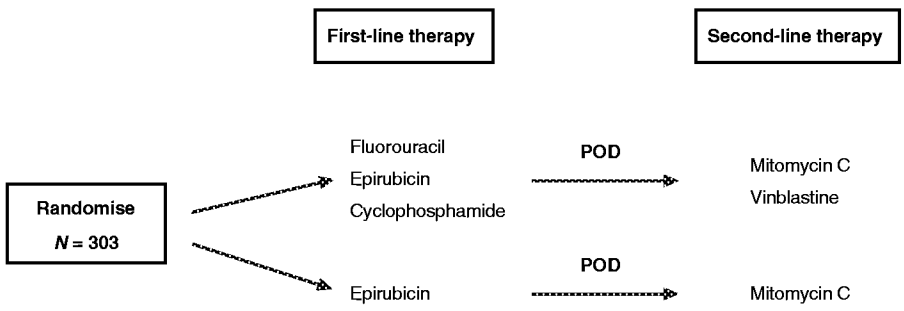

Fig. 1. Randomised trial comparing combination chemotherapy with sequential single-agent therapy. POD: progression of disease.

Pending further prospective randomised trials, both combination therapy and sequential single-agent therapy remain valuable options in the treatment of patients with metastatic breast cancer. Clinical decision-making in this context ultimately relies upon both the science and the art of medical oncology.

Declared interests

The authors have declared that no conflicts of interest exist.

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