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Combination of taxanes and anthracyclines in first-line chemotherapy of metastatic breast cancer: an interim report

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Abstract

Anthracyclines and taxanes are among the most effective agents in the treatment of advanced breast cancer, refractory or non-responsive to endocrine manipulation. Several recently published phase III studies have addressed the role of these compounds in combination compared with established chemotherapy regimens. This report considering a total of 4244 patients evaluates the data of those trials with respect to the efficacy and toxicity of the treatment regimens. Currently, evidence is growing that especially patients with symptomatic visceral tumour spread may benefit from the combined application of anthracyclines and taxanes. Adequately dosed polychemotherapy appears to be more successful than monotherapy, and, at present, the combination of anthracyclines (doxorubicin, epirubicin) and taxanes (docetaxel (Doc), paclitaxel (Pac)) might lead to a promising approach to improve the course of the metastatic disease. © 2002 Published by Elsevier Science Ltd.

Keywords: Metastatic breast cancer; First-line treatment; Combination chemotherapy; Taxanes; Anthracyclines; Docetaxel; Paclitaxel; Doxorubicin; Epirubicin

1. Introduction

Breast cancer is the most common malignant disease in women of the Western industrialised nations. Despite adequate primary therapy, many patients with apparently localised disease harbour subclinical micrometastases that may grow to clinically relevant macrometastases later on. Until now, metastasised mammary carcinoma remains essentially incurable and will lead to death after a median survival period of 2–3 years [1]. The time interval may vary considerably in individual cases, resulting in approximately 10% of patients requiring continuous or intermittent systemic treatment for 10 or more years [2]. On the background of incurability, palliation of the disease-related complaints is an urgent task. Tumour-associated pain, fatigue and depressive conditions may be found in numerous patients. Dyspnoea, cough and anorexia are direct correlates to the individual tumour burden. Thus, maximal reduction of symptoms caused by the disease is the ultimate goal of palliative care. Occasionally, therapy has to be considered in patients without clinical symptoms in order to avoid the evolvement of life-threatening complications (i.e. organ failure).

While patients with hormone receptor-positive tumours are typically treated with endocrine therapy, primary chemotherapy is indicated in patients with rapidly growing visceral metastases or hormone receptor-negative disease. This is also justified in those cases that become refractory to endocrine therapy. The percentage of unselected patients whose metastatic disease responds to systemic chemotherapy is almost twice as large as the success rate of endocrine treatment [3]. There are continuous efforts to develop treatment strategies for early and advanced breast cancer. Innovative cytotoxic or endocrine active agents have to be tested individually in phase II and in prospective randomised phase III trials before wider use or even combined clinical application is warranted. After these steps have been successfully taken, the new agents may be integrated in combination regimens for first-line treatment. Finally, promising compounds are evaluated in randomised trials in comparison with standard treatment in the adjuvant setting. This sequential approach together with meta-analyses of the resulting clinical data has led

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to the standard recommendations currently in use for the treatment of early breast cancer [4]. However, for metastatic breast cancer, no such standard has so far been established.

Alkylating agents and antimetabolites were the first cytotoxic substances introduced successfully in the chemotherapy of advanced breast cancer (i.e. cyclophosphamide/methotrexate/5-fluoro-uracil first individually, and later on in combination) [5]. In the 1970s and 1980s, striking advances were achieved by introduction of the anthracylines doxorubicin [6] and epirubicin into systemic therapy. It was demonstrated then that anthracyclines improved the response rates in cases of advanced disease [7] and the survival of early breast cancer patients [8]. Consequently, anthracyclines were integrated into the adjuvant setting, and also in combination therapy.

A decade ago, the taxanes paclitaxel (Pac) (Taxol®) and docetaxel (Doc) (Taxotere®) were found to be very active agents in patients with advanced breast cancer [9]. Both compounds inhibit cell growth by interfering with essential steps in the correct assembly of microtubules, leading to mitotic arrest. After their impressive antitumour activity became apparent, they were combined with the established anthracycline therapy of metastasised mammary cancer. A plethora of phase II trials have been published on this issue in recent years. In order to define the clinical relevance of this highly active combination for advanced disease, the response rates have to be evaluated together with the side-effects. Thus, a survey on several prospective phase III trials is warranted, including the comparison of the new combinations with various established regimens, containing anthracyclines. This article compiles and evaluates the data of the recently published reports on the efficacy and the toxicity of the combined application of anthracyclines and taxanes in first-line therapy.

2. Trials with anthracyclines and taxanes used as single applications

Comparative phase III studies on the monotherapy of advanced breast cancer with anthracyclines versus taxanes were prerequisites for introducing the simultaneous application of members from both families of cytotoxic compounds (Table 1). In a two-armed study [10], the efficacy of doxorubicin was evaluated in comparison with docetaxel in first-line treatment of advanced mammary carcinoma. 326 patients were randomised to receive either doxorubicin (A 75 mg/m^2) or docetaxel (Doc 100 mg/m^2). Preceding chemotherapy with alkylating agents was one of the major inclusion criteria in this study. Since 95 (58%) of the patients in the doxorubicin group and 79 (49%) of the patients in the docetaxel arm had been treated previously with alkylating

Table 1
Prospective randomised phase III studies comparing doxorubicin (A) monotherapy with docetaxel (Doc) or paclitaxel (Pac) in the first-line treatment of metastatic breast cancer

Author	Design	Patients					Response		
		n	Recurrence-free interval[a]	⩾3 Metastatic sites (%)	Visceral metastases (%)	Chemonaïve (%)	CR + PR (%)	TTP[b]	OS[c]
Chan and colleagues, (1999) [10]	A (75 mg/m^2) versus Doc (100 mg/m^2)	326	26 versus 27	43 versus 44	76 versus 75	58 versus 49	33 versus 48 ($P=0.008$)	4.3 versus 6.5 (n.s.)	14 versus 15 (n.s.)
Paridaens and colleagues 2000) [11]	A (75 mg/m^2) versus Pac (200 mg/m^2/$_{3h}$)	331	33 versus 24	32 versus 28	56 versus 63	67 versus 68	41 versus 25 ($P=0.003$)	7.5 versus 3.9 ($P<0.001$)	18.3 versus 15.6 (n.s.)

CR, complete remission; PR, partial remission; TTP, time to progression; OS, overall survival; n.i., not indicated; n.s., non significant.
[a] Median interval between diagnosis and first recurrence (months).
[b] Median time to progression (months).
[c] Median overall survival (months).

Table 2
Haematological or non-haematological toxicity and therapy-associated mortality in phase III trials comparing doxorubicin (A) monotherapy with docetaxel (Doc) or paclitaxel (Pac) in the first-line treatment of metastatic breast cancer

Design	Haematological toxicity (% of patients)			Non-haematological toxicity (% of patients)			Mortality (*n*)
	Neutropenia (grade 3/4)	Febrile neutropenia	Infection (grade 3/4)	Neurotoxicity (grade 3/4)	Cardiotoxicity (CHF)	Emesis	
A (75 mg/m^2) versus Doc (100 mg/m^2)	94 versus 89	6 versus 12 ($P<0.05$)	3 versus 4 n.s.	10 versus 0 ($P<0.001$)	0 versus 4 ($P<0.001$)	3 versus 12 ($P<0.05$)	1 versus 3 n.s.
A (75 mg/m^2) versus Pac (200 mg/m$^2_{3h}$)	85[a] versus 40[a] ($P<0.001$)	20 versus 7 ($P<0.001$)	6 versus 4 n.s.	0 versus9 ($P<0.001$)	4 versus 0 ($P=0.015$)	13 versus 2 ($P<0.001$)	3 versus 0 n.s.

CHF, congestive heart failure; n.i., not stated; n.s., non significant.
[a] Neutropenia grade IV.

agents for metastatic disease, less than half of the patients underwent therapy in a genuine first-line setting. That study was the first to demonstrate the superiority of the cytotoxic agent docetaxel over the 'gold standard' doxorubicin applied in the highest feasible dosage. The response rates for docetaxel were significantly higher than for doxorubicin (48% versus 33%, $P=0.008$). Furthermore, docetaxel was clearly more active in patients with visceral metastases (46% versus 29%) and in cases that showed resistance to prior chemotherapy (47% versus 25%; data not presented in Table 1). Toxicity was acceptable demonstrating substance-specific side-effects for each compound (Table 2).

Recently, Paridaens and co-workers [11] published the results of a European phase III trial on first-line monotherapy of advanced breast cancer, in which 331 patients were randomised and treated with doxorubicin (75 mg/m^2) or paclitaxel (200 mg/m^2/$_{3h}$). Up to seven cycles of chemotherapy were applied in 3-weekly intervals. On progression or resistance of the disease, the patients received the comparator as the next step of systemic chemotherapy ('cross-over') in order to find the optimum sequence for the two drugs under investigation. The primary aim of the study was the evaluation of progression-free survival and possible cross-resistance in the second-line setting. The response rates were significantly higher for doxorubicin than for paclitaxel in the first-line treatment (41% versus 25%). Irrespective of the sequence of application, there was no total cross-resistance which is reflected by the response rates to second-line therapy (30% for A and 16% for Pac, respectively; not shown in Table 1). Incidence and grade of toxicity, except for neurotoxicity, were higher in the doxorubicin arm. However, based on the mitigation of tumour-related symptoms, the authors concluded that a superior palliation was achieved by the treatment with anthracycline as opposed to paclitaxel. Both studies demonstrated the high efficacy of anthracyclines and taxanes in the monotherapy of advanced breast cancer, although they were inconclusive as to the most effective taxane. These precursor trials with single agents were followed by a number of studies dealing with the simultaneous application of anthracyclines and taxanes [14–21]. The development was fuelled by the results of several phase II trials demonstrating the applicability and activity of the combination.

3. Studies on the combination of anthracyclines and taxanes in first-line treatment

One of the pioneering trials in this field was conducted by Gianni and co-workers [12] who applied a 3-h infusion of paclitaxel together with a bolus injection of doxorubicin (60 mg/m^2) in a cohort of 35 chemonaïve patients. The dose of Paclitaxel in this one-armed, dose-finding phase II study was increased stepwise from 125 to 200 mg/m^2. The authors reported on impressive response rates exceeding 90%, which were not reproducible in subsequent phase III trials performed by other groups. With respect to cardiotoxicity, a clinically relevant reduction of the ventricular ejection fraction was apparent in 20% of the patients in the Gianni study, after a median cumulative dose of approximately 480 mg/m^2 doxorubicin was reached. Thus, the reduction of cardiac side-effects of the doxorubicin/paclitaxel combination was a major issue in subsequent studies using various schedules and sequential approaches in the simultaneous application of both compounds [13].

Within the last 2 years, the results of a number of phase III studies for the first-line treatment of metastatic breast cancer have been reported, comparing the combination of anthracyclines and taxanes with established anthracycline-containing regimens [14–21]. In order to facilitate the critical evaluation of the various trials, the main data concerning efficacy and toxicity were compiled (Table 3 and 4).

3.1. Studies with docetaxel and anthracyclines

An international trialist's group headed by Nabholtz [14] compared the ADoc regimen (doxorubicin/docetaxel, 50 and 75 mg/m^2, respectively) with the AC regimen (doxorubicin/cyclophosphamide 60 and 600 mg/

Table 3
Prospective randomised phase III studies with combinations of anthracyclines and taxanes in the first-line treatment of metastatic breast cancer

Author	Design (doses in mg/m^2)	Patients					Response		
		n	Visceral metastases%	⩾3 Metastatic sites (%)	Chemonaïve (%)	Recurrence-free interval[a]	CR + PR (%)	TTP[b]	OS[c]
Nabholtz and colleagues, (1999) [14]	ADoc (50/75) versus AC (60/600)	439	61 versus 64	39 versus 42	56 versus 60	24 versus 25	60 versus 47 ($P = 0.012$)	9.3 versus 8 ($P = 0.0153$)	n.s.
Nabholtz and colleagues, (2001) [15]	DocAC (75/50/500) versus FAC (500/50/500)	484	74 versus 72	47 versus 48	n.i.	n.i.	54 versus 43 ($P = 0.023$)	n.i.	n.i.
Bonneterre and colleagues (2001) [16]	EDoc (75/75) versus F[d] EC (500/75/500)	141	n.i.	36 versus 41	67 versus 61	>12	62.5 versus 31.3 ($P < 0.05$)	8.6 versus 6.1 ($P < 0.05$)	n.i.
Sledge and colleagues (1997) [17]	APac ($50/150_{24h}$ + GCSF) versus A (60) versus Pac (175_{24h})	739	n.i.	n.i.	n.i.	69	46 versus 34 versus 33	8.0[e] versus 6.2 versus 5.9	22.4 versus 20.1 versus 22.2 (n.s.)
Biganzoli and colleagues (2000) [18]	APac ($60/175_{3h}$) versus AC (60/600)	271	85 versus 81	26 versus 25	64 versus 63	24 versus 32	58 versus 54 (n.s.)	5.9 versus 6.0 (n.s.)	n.i.
Lück and colleagues (2000) [19]	EPac ($60/175_{3h}$) versus EC (60/600)	541	78 versus 71	n.i.	68 versus58	n.i.	46 versus 40 (n.s.)	9.0 versus 7.4 (n.s.)	16.8 versus 20.3. (n.s.)
Carmichael and colleagues (2001) [20]	EPac (75/200) versus EC (75/600)	705	approximately 90	n.i.	46	35.3	40 versus 37 (n.s.)	6.5 versus 6.8 (n.s.)	13.7 versus 13.8 (n.s.)
Jassem and colleagues (2001) [21]	A→Pac ($50 \rightarrow 220/_{3h}$) versus F[d] AC (500/50/500)	267	64 versus 68	n.i.	56 versus 54	20.7 versus 22.5	68 versus 55 ($P = 0.032$)	8.3 versus 6.2 ($P = 0.034$)	23.3 versus 18.3 ($P = 0.0134$)

GCSF, granulocyte colony stimulating factor; CR, complete remission; PR, partial remission; TTP, time to progression; OS, overall survival; ADoc, anthracycline = doxorubicin/docetaxel; AC, doxorubicin/cyclophosphamide; FAC, 5-fluoro-uracil/doxoribicin/cyclophsophamide; APac, anthracycline = doxorubicin/paclitaxel; FEC, 5-fluoro-uracil/epirubicin/cyclophosphamide; n.i., not indicated; n.s., not significant.

[a] Median interval between diagnosis and occurrence of metastases (months).

[b] Median time to progression (months).

[c] Median overall survival (months).

[d] 5-Fluoro-uracil.

[e] Median number of months to treatment failure (significantly longer for APac versus A or Pac respectively).

Table 4
Haematological or non-haematological toxicity and therapy-associated mortality in phase III trials combining anthracyclines and taxanes in the first-line treatment of metastatic breast cancer

Design (doses in mg/m^2)	Haematological toxicity (% of patients)			Non-haematological toxicity (% of patients)				Mortality (n)
	Neutropenia (grade 3/4)	Febrile neutropenia	Infection (grade 3/4)	Neurotoxicity (grade 3/4)	Arthralgia, myalgia	Cardiotoxicity CHF	Emesis (grade 3/4)	
ADoc (50/75) versus AC (60/600)	82 versus 69 ($P<0.05$)	33 versus 7 ($P<0.05$)	8 versus 2 ($P=0.01$)	0 versus <1	n.i.	3 versus 4	6 versus 6	1 versus 3
DocAC (75/50/500) versus FAC (500/50/500)	94 versus 81	29 versus 4	5 versus 3	0	n.i.	5 versus 7	5 versus 7	3 versus 2
EDoc (75/75) versus FEC (500/75/500)	67 versus 58	26 versus 0	5 versus 0	3 versus 0	n.i.	1 versus 0	17 versus 19	1 versus 0
APac ($50/150_{24h}$+GCSF) versus A (60) versus Pac (175_{24h})	n.i.	n.i.	n.i.	n.i.		9 versus 9 versus 4	n.i.	6 versus 2 versus 4 (n.s.)
APac ($60/175_{3h}$) versus AC (60/600)	89 versus 81	32 versus 9 ($P<0.05$)	7 versus 3	3 versus 1	7 versus 0 ($P<0.05$)	3 versus 1	7 versus 18 ($P<0.05$)	0 versus 1
EPac ($60/175_{3h}$) versus EC (60/600)	64 versus 60	0 versus 0	5 versus 4	4 versus 1	n.i.	1 versus 0	3 versus 6	0
EPac (75/200) versus EC (75/600)	n.i.	n.i.	14 versus 11	5 versus 1 $P=0.003$	n.i.	1 versus 0	n.i.	n.i.
A→Pac ($50\rightarrow220/_{3h}$) versus FAC (500/50/500)	89 versus 65 ($P<0.001$)	8 versus 5 (n.s.)	2 versus 0 (n.s.)	12 versus 0 ($P<0.001$)	10 versus 0 ($P<0.001$)	2 versus 1 (n.s.)	8 versus 19 ($P=0.018$)	1 versus 1

CHF, congestive heart failure; n.i., not indicated; n.s., not significant; ADoc, anthracycline=doxorubicin/docetaxel; AC, doxorubicin/cyclophosphamide; FAC, 5-fluoro-uracil/doxoribicin/cyclophsophamide; APac, anthracycline=doxorubicin/paclitaxel; FEC, 5-fluoro-uracil/epirubicin/cyclophosphamide.

m^2) as first-line combination chemotherapy applied in 3-weekly intervals (Table 3). Recruitment for this phase III study (TAX306) took place between 6/96 and 3/98. The docetaxel-containing regimen revealed significantly better response rates and a longer interval to progression as opposed to the AC arm. This is remarkable because the anthracycline dose was ca. 20% lower in the cohort treated with ADoc than in the AC arm, and yet a higher response was achieved using ADoc than with AC. In most of the following studies, equivalent doses of the anthracycline were used in both treatment arms. The TAX306 study demonstrated that the ADoc combination was superior in the treatment of patients who had previously received adjuvant chemotherapy or were suffering from prognostically poor visceral metastases. Although there was a difference in response between the ADoc and AC arms, it was not possible to determine any survival advantage due to the lack of a sufficient observation time. In terms of toxicity (Table 4), there were significantly more patients suffering from febrile or non-febrile neutropenia and infection during treatment with ADoc than under therapy with AC. However, this did not provoke a comparable increase of sepsis-associated deaths (1 case in the ADoc arm versus 3 cases in the AC arm). The incidence of clinically relevant cardiac dysfunctions was relatively low in both treatment arms.

An initial analysis of the subsequent study (TAX307; DocAC versus 5-fluoro-uracil/doxorubicin/cyclo-phosphamide (FAC); Tables 3 and 4) of the Breast Cancer International Research Group (BCIRG) was presented by Nabholtz [15] at the 2001 American Society of Clinical Oncologists (ASCO) meeting. Time to progression analysis was not feasible, because at that time the number of recurrences required for the statistical evaluation was not reached. Hence, the results of the study were confined to preliminary data concerning response and toxicity only. In accordance with the previous TAX306 study, the DocAC regimen in TAX307 produced significantly higher response rates than the FAC combination chemotherapy (54 versus 43%; $P=0.023$). The authors concluded that the combination of three cytotoxic compounds in each treatment arm did not lead to a significant rise in side-effects (Table 4).

A third trial group presented by Bonneterre and colleagues [16] at the 2001 ASCO meeting preferred the anthracycline epirubicin, which is presumably less cardiotoxic than doxorubicin. The dose of 75 mg/m^2 epirubicin was applied in combination with 75 mg/m^2 docetaxel in the phase III setting. The comparative cohort was treated with $FE_{75}C$ thus containing the same dose of epirubicin as in the EDoc arm. The patients eligible for this study had a recurrence-free interval exceeding 12 months after completion of the preceding adjuvant treatment. Granulocyte colony stimulating factor (GCSF)-support was given to 19% of the patients receiving EDoc. In accordance with the two prior studies on combination

chemotherapy with taxanes, the EDoc arm was associated with a higher response rate than the comparator (62.5 versus 31.3%; $P < 0.05$; Table 3). The results of this study were regarded by the trialists as promising enough to extend the approach to the adjuvant setting.

3.2. Studies combining paclitaxel with anthracyclines

Sledge and colleagues presented results of a multicentre phase III study for the first-line setting at the 1997 ASCO meeting [17]. This three-armed trial (Tables 3 and 4) including 739 patients compared the efficacy of the combination of doxorubicin (50 mg/m^2) and paclitaxel (150 mg/m^2/$_{24h}$) applied with GCSF-support with appropriate monotherapies containing doxorubicin (60 mg/m^2) or paclitaxel (175 mg/m^2/$_{24h}$). Unfortunately, no final report has appeared to date, so that detailed data on the toxicity and the subgroup analyses are not available at present. The results of the combination therapy with anthracycline doxorubicin/paclitaxel (APac) demonstrate a significantly higher antitumour activity ($p < 0.05$) in terms of response rate (46% for APac versus 34 or 33% for monotherapy with A or Pac, respectively) and time to treatment failure (8.0 months versus 6.2 months or 5.9 months for A or Pac, respectively). There was no improvement in long-term survival for any of the treatment subgroups.

At the 2000 ASCO meeting, Biganzoli and colleagues [18] presented another study dealing with the combination of doxorubicin and paclitaxel as first-line treatment (APac versus AC; Tables 3 and 4). In addition to the evaluation of efficacy, one of the aims of this study was the reduction of cardiotoxicity that had raised serious concerns in phase I/II trials using an identical combination of compounds [13]. Thus, in the Biganzoli study the cumulative dose of doxorubicin was limited to a maximum of 360 mg/m^2 (six cycles) in both treatment arms. The majority (approximately 80%) of the patients included in this trial had visceral metastases, indicating a high-risk situation. The response to the APac combination was almost identical as in the cohort receiving AC, as was the time to progression. However, the incidence of febrile neutropenia was more than triple in the APac arm as opposed to patients given AC therapy (32% versus 9%). In addition, there was a decrease in the left ventricular ejection fraction observed in 27% of the APac patients versus 14% in the AC arm of the study (data not shown in Table 4). Thus, with respect to the haematological and cardiac side-effects of the APac treatment and given the similar response rates in both treatment arms, there was no clinically relevant advantage for the paclitaxel-containing regimen.

In the multicentre trial of the German Arbeitsgemeinschaft für gynäkologische Onkologie (AGO) [19], 541 patients were randomised in a first-line setting to receive either the combinations of epirubicin and paclitaxel (60 and 175$_{3h}$ mg/m^2) or epirubicin and cyclophosphamide (60 and 600 mg/m^2) in 3-weekly intervals. The response rates (46 versus 40%) and the time to progression (9.0 versus 7.4 months) were slightly better in the EPac than after epirubicin/cyclophosphamide. However, there was a small advantage in the median overall survival time favouring the epirubicin/cyclophosphamide (EC) arm (20.3 versus 16.8 months in the EPac subgroup), but this was non significant. From the data presented, it appeared that the EPac combination was slightly more active in patients who had been previously treated with adjuvant chemotherapy. This is not surprising, since most of these patients had failed in the preceding regimen with alkylating agents, rendering the proportion of chemonaïve patients 10% higher in the EPac arm than in the EC subgroup (68% versus 58%). Therefore, the patients in the EC arm might have been less responsive to the first-line cyclophosphamide-containing EC treatment. The slightly higher overall survival rate in the EC arm may be due to the influence of salvage therapy applied in second-line, possibly containing taxanes. Another point is the aspect of under-dosage of epirubicin in the EC group (60 instead of 90 mg/m^2 in conventional epirubicin therapy). Finally, the therapeutic value (ratio of efficacy and toxicity) of the EPac combination was notable only because very few patients experienced severe haemato- or cardiotoxicity.

Carmichael and colleagues [20] added further evidence to the ambiguous role of paclitaxel in combination with epirubicin in the first-line treatment of breast cancer. In their multicentre trial, the doses of epirubicin (75 mg/m^2) and paclitaxel (200$_{3h}$ mg/m^2) in EPac were 25% higher than those used in the German trial of the AGO. The other arm in this UK study was 75 mg/m^2 epirubicin and 600 mg/m^2 cyclophosphamide, which is the same as in the trials of Biganzoli and the German trial. Consistent with the two previous studies, Carmichael and colleagues reported similar response rates in both treatment arms (40% versus 37%). Time to progression of the disease was comparable in the last-mentioned studies; overall survival was equivalent in the last two studies. Compared with the German trial, the escalation of doses in the UK study provoked a significant increase in therapy-associated toxicity as shown by the clinically relevant number of infections in both treatment arms (14 and 11%, respectively).

In the two-armed phase III study conducted by Jassem and colleagues [21], paclitaxel and doxorubicin (50 mg/m^2 A→Pac 220 mg/m^2/$_{3h}$) were combined in such way that the anthracycline bolus was followed 1 day later by the paclitaxel infusion. With 3-weekly intervals, the procedure was repeated six times, unless the patients progressed. This regimen was compared with the triple combination of FAC (500/50/500). In addition to the extended time to progression (8.3 months versus 6.2 months), superior response rates (68% versus 55%) and

longer overall survival (23.3 months versus 18.3 months) were observed in the paclitaxel-treated cohort. 24% of the patients primarily treated with FAC received a taxane as subsequent salvage therapy. Febrile neutropenia was an infrequent problem in this study (A→Pac in 8 cases versus FAC in 5 cases). Nausea and vomiting occurred more often in the FAC arm, whereas neurotoxicity and arthralgia/myalgia were primarily associated with the paclitaxel-containing combination. Finally, the gain in overall survival in the A→Pac treatment arm was unique among the trials listed in our survey and may be indicative of the potential of taxanes to extend the metastatic breast cancer patient's lifespan.

4. Discussion

Adequate palliative chemotherapy is aimed at reducing tumour-related symptoms and may profoundly improve the general condition of patients suffering from metastatic disease [22]. However, its efficacy on overall survival appears to be rather modest for the time being. The sites and extent of metastatic deposits determine the patient's individual risk and expectations for remission. Moreover, these factors influence the patient's willingness to accept the side-effects of systemic treatment regimens. Therapy-associated toxicity ought to be more than counterbalanced by relief from symptoms. This applies equally to single or combination chemotherapy. Thus, the application of palliative chemotherapy may be considered for each case. Currently, it is a difficult choice to decide, whether it is more useful to adopt a regimen that is less toxic and presumably less active, instead of a therapy with a higher response rate at the expense of an increased risk of toxicity [23]. Solutions to the dilemma can be aided by precise estimation and evaluation of the individual risk situation of the patient.

In this survey on more than 3500 patients, eight phase III trials were evaluated with the purpose to extract the possible benefits of combination chemotherapy with anthracyclines and taxanes. The studies analysed were comparable in that similar inclusion criteria and therapy regimens had been applied. However, looking at the details, the trials were heterogeneous with respect to the doses and schedules of the compounds used in the combinations tested. The comparison arms varied from study to study, except for the AC combination that was applied by Nabholtz and colleagues [14] and Biganzoli and colleagues [18].

A series of additional clinically relevant factors and inclusion criteria may limit comparisons of the data:

- Number of patients included,
- Extent of disease-free interval,
- Preceding adjuvant treatment (chemotherapy/endocrine therapy),
- Number and proportion of patients pre-treated with adjuvant chemotherapy,
- Location of metastases (i.e. visceral/multivisceral disease),
- Follow-up intervals,
- Quality of salvage therapy.

Although only some of these variables were defined in the trials examined, preliminary conclusions may be drawn:

- The response rates in combination chemotherapy tend to be higher than those achieved with the corresponding single agents, although lower dosages of anthracyclines were applied in some combinations. This may suggest some type of cooperation between the agents used.
- But, there are no stringent indications of additive or synergistic effects in the combinations of taxanes and anthracyclines with respect to the response rates and time-to-progression.
- Patients with high-risk visceral metastases appear to derive benefit from the combination therapies with taxanes, although meta-analyses were not presented.
- The incidence of therapy-related side-effects is generally increased following combination therapy compared with single drug applications. This was most obvious for febrile neutropenia.
- Treatment-associated mortality is apparently a rare event and is not increased by the combination therapies compared with single agent use.

Discriminating the efficacy and toxicity of the two taxanes, docetaxel and paclitaxel, appears complex, since, as yet, there are no data available allowing a direct comparison. Three of the studies demonstrated that combinations with docetaxel yielded higher response rates than the comparative regimens. However, three of four paclitaxel-containing regimens achieved similar anti-tumour activity as the corresponding established combinations with anthracyclines. Possibly due to the intricate design, the study of Jassem and colleagues [21] reached a substantial overall survival benefit with the combination of A→Pac. The conclusions drawn from this review on the present state of trials dealing with combination chemotherapy concur with the generally slow and troublesome progress that has been made in the treatment of metastatic breast cancer [24,25].

Several attempts have been considered to reduce the haematotoxicity of monotherapy by changing the application from 3-weekly to weekly administration. Alteration of regimens to weekly administrations of 35 mg/m^2 reduced severe neutropenia (grades 3 and 4) from the approximately 90% seen after 100 mg/m^2 in three-weekly applications to approximately 9%, while

grade 4 neutropenia was no longer observed [26]. Similar effectiveness with relatively mild haematological toxicity was observed following combination chemotherapy consisting of the weekly application of 25 mg/m^2 epirubicin and 30 mg/m^2 docetaxel [27], or of 50 mg/m^2 doxorubicin on day 1 followed by the fractionated, weekly 36 mg/m^2 docetaxel as had been shown before in Ref. [28]. The rate of alopecia appeared to be increased in all of these fractionation trials.

With respect to the limited budget of healthcare systems, the cost-effectiveness of therapy is of particular interest in the treatment of metastatic breast cancer [29,30]. The combined application of anthracyclines and pacitaxel is estimated to be approximately 10% more expensive than monotherapy with pacitaxel. This may be explained by the grossly unchanged paclitaxel dose in combination compared with monotherapy. In contrast, expenses for the combined application of anthracyclines and docetaxel appear to be less costly by approximately 10% since the docetaxel dosage is reduced by approximately 25% in the combination (Table 3). In cases of non-response to the combination therapy with anthracyclines and taxanes, monotherapy with vinorelbine, capecitabine, gemcitabine and trastuzumab (Herceptin®) may be added [31].

Further steps toward optimising the treatment schedules will include combining chemotherapy with the therapeutic principles of very different modes of action, such as target-specific antibodies against cell surface receptors of growth factors [32], or inhibitors of tyrosine kinases in pathways of signal transduction [33–35]. Future trends in the field may take advantage of the wide spectrum of upcoming diagnostic and therapeutic approaches based on an increased knowledge of the genetic make-up and gene expression profiles [36,37] of cancer cell populations in individual patients. However, it will remain paramount to improve the treatment of breast cancer by combining the most active compounds with a minimum of side-effects in early and in selected cases with advanced disease.

Note added in proof

The observations by Biganzoli et al [18] have been confirmed in a most recent publication [38].

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