Taxanes in the first-line chemotherapy of metastatic breast cancer: Review

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Summary

Taxanes belong to the most effective agents in the treatment of advanced and non-hormone responsive breast cancer. Several recently published phase III studies have examined the role of taxane-anthracycline combinations in the first line treatment of metastatic breast cancer. Especially, patients with symptomatic visceral spread seem to benefit from taxanes containing polychemotherapy that is adequately dosed. Polychemotherapy with taxanes appears to be more effective than monotherapy. But at present, there are no adequate data concerning the comparison of taxane-monotherapy and anthracycline-containing polychemotherapy. New hopeful results with respect to efficacy and toxicity are reported from the docetaxel-capecitabine polychemotherapy. Thus, the combination of anthracyclines (adriamycin, doxorubicin) and taxanes (docetaxel, paclitaxel) is a promising tool in the treatment of metastatic breast cancer. New interesting combinations are under investigation.

Key words: Breast cancer; Metastases; Chemotherapy; Taxanes.

Introduction

Despite advances in locoregional treatment and systemic adjuvant therapy for breast cancer, the recurrence rate is indicated to be a remarkable 40% after adjuvant polychemotherapy. So far, metastatic breast cancer remains essentially incurable and will lead to death after a median survival period of two of three years [1]. For patients with advanced hormone receptor positive breast cancer, endocrine therapy as well as chemotherapy can provide palliation. But, for patients with hormone receptor negative and symptomatic metastatic breast cancers, chemotherapy is generally the first treatment option in order to achieve a maximal reduction of complaints caused by the disease as the ultimate goal of palliative care.

Alkylating agents and antimetabolites were the first cytotoxic substances introduced successfully in the chemotherapy of metastatic breast cancer. Since their introduction in the early 1970s, anthracyclines (doxorubicin, epirubicin) have generally been considered to be more active chemotherapeutic agents in the treatment of metastatic breast cancer. It has been demonstrated that anthracyclines improved the response rates of metastatic breast cancer [2, 3]. In particular, in patients with metastatic breast cancer and after alkylating agent chemotherapy, doxorubicin monotherapy has produced response rates of 25% to 33% at doses ranging from 60-75 mg/m^2 with median times to progression between 2.7 and 4.5 months, while monotherapy with epirubicin or mitoxantrone have not further improved these results [3-10]. Because of improving the survival of early breast cancer, anthracyclines were integrated in the adjuvant setting.

In phase II studies, taxanes have been found to be very active in the treatment of metastatic breast cancer especially in patients with visceral involvement, liver metastasis and resistance to previous treatment. Response rates of 43% to 61% were reported in patients with or without previous anthracycline therapy [11-13]. Both paclitaxel and docetaxel inhibit cell growth by interfering with the process of correct assembly of microtubules with the result of mitotic arrest. Because of their high antitumor activity in metastatic breast cancer patients, several trials were initiated investigating the combination of taxanes with established anthracyclines in the therapy of metastatic breast cancer. The clinical relevance of highly active combination therapy for metastatic breast cancer depends on the side-effects on the one hand and on the response rates on the other hand. Thus, this article evaluates the recently published data concerning the efficacy and the toxicity of the combined application of anthracyclines and taxanes in first-line therapy.

Anthracyclines and taxanes as single applications

In the EORTC-trial [14] as a first-line single agent chemotherapy study for metastatic breast cancer, 331 patients were randomized to receive either paclitaxel 200 mg/m^2 as 3-hour infusion every three weeks or doxorubicin 75 mg/m^2 intravenous bolus every three weeks for a planned seven courses unless progression or unacceptable toxicity occurred. For patients with early progression, cross-over to the alternative drug was planned. The

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objective response rate (ORR) in the first-line therapy was significantly better (p = 0.003) for doxorubicin than for paclitaxel (ORR: 41% vs 25%), with doxorubicin achieving a longer median progression-free survival (7.5 months for doxorubicin versus 3.9 months for paclitaxel, p = 0.001). In second-line therapy, crossover to doxorubicin and to paclitaxel gave response rates of 30% and 16%, respectively. The median durations of survival of 18.3 months for doxorubicin and of 15.6 months for paclitaxel were not significantly different.

The results of the monotherapy arms of the American Intergroup trial [15] are difficult to compare with those of the EORTC-trial because the Intergroup used a lower dose of doxorubicin and a different dose and schedule of administration of paclitaxel [14]. The American Intergroup, however, reported that first-line paclitaxel produced very similar response rates, time to progression (TTP) and overall survival compared with doxorubicin. This study also featured a crossover component in which patients progressing on one single agent received the other drug upon disease progression. The response rate for salvage paclitaxel was less than 20%. The ideal dose and schedule of paclitaxel are yet to be defined. Using the 3-hour infusion, increasing the dose of paclitaxel from 175 mg/m^2 up to 250 mg/m^2 does not significantly improve efficacy but does increase toxicity. Prolonging the duration of infusion of paclitaxel from three to 24 hours at a fixed dose of 250 mg/m^2 results in higher response rates without improving progression-free survival or overall survival.

In the prospective randomized phase III trial of Chan *et al.* [16] docetaxel (100 mg/m^2 every three weeks) monotherapy is compared with doxorubicin (75 mg/m^2 every three weeks) monotherapy in patients with metastatic breast cancer who had received previous alkylating-agent containing chemotherapy. The objective response rate was significantly higher in the docetaxel arm compared with the doxorubicin arm (47.8% vs 33.3%; p = 0.008). Docetaxel was also significantly more active than doxorubicin in patients with negative prognostic factors, such as visceral metastases (ORR: 46% vs 29%) and resistance to prior chemotherapy (ORR: 47% vs 25%). Median time to progression was longer in the docetaxel group (26 weeks vs 21 weeks), but the difference was not significant. Median overall survival was similar in the two groups (docetaxel: 15 months; doxorubicin: 14 months). Concerning toxicity, there were four deaths due to cardiotoxicity in the doxorubicin group, while there was one death due to infection in both the docetaxel group and the doxorubicin group. The incidences of febrile neutropenia and severe infection as well as of non-hematologic toxicities (nausea, vomiting, stomatitis and cardiac toxicity) were higher among patients receiving doxorubicin, whereas diarrhea, neuropathy, fluid retention, and skin and nail changes were higher among patients receiving docetaxel.

All studies demonstrated the high efficacy of anthracyclines and taxanes in the monotherapy of metastatic breast cancer. These studies were not really conclusive regarding the question as to which one of the taxanes is the most effective. Thus, docetaxel monotherapy appears to have at least equivalent efficacy and possibly a superior toxicity profile compared with doxorubicin. To date, docetaxel remains the only single agent that has demonstrated superior response rates compared with doxorubicin.

Comparing taxanes containing monotherapy to polychemotherapy

Three subsequent phase III trials in patients previously treated with anthracyclines compared single agent docetaxel with polychemotherapy (mitomycin C/vinblastine; methotrexat/5-FU; vinorelbine/5-FU) [17-19]. In these studies, docetaxel was shown to increase response rates with the exception of the comparison of docetaxel with vinorelbine/5-FU. In a previously published first-line phase II trial in breast cancer patients treated with alkylating agents, docetaxel is compared with standard polychemotherapy epirubicin/cyclophosphamid demonstrating similar response rates and time to progression in both arms. Thus, these randomized data show that docetaxel seems to be the most active single agent against metastatic breast cancer. Moreover, these studies confirm the incomplete clinical cross-resistance between docetaxel and anthracyclines.

Combinations of anthracyclines and taxanes in first-line treatment

Within the last two 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. In three randomized trials docetaxel/anthracycline combinations are compared with standard polychemotherapy. The first study [21] evaluated the doxorubicin/docetaxel (AT) regimen and the doxorubicin/cyclophosphamide (AC) regimen as first-line therapy for metastatic breast cancer. The docetaxel-containing regimen revealed significantly better response rates (59% vs 47%) and time to progression (37 weeks vs 32 weeks) compared with the AC-arm. This is remarkable because the anthracycline dose was about 20% lower in the AT-arm than in the AC-arm. Furthermore, the AT-combination demonstrated higher response rates than the AC-combination especially in patients with previously adjuvant chemotherapy or with poor prognosis suffering from visceral metastases. Concerning toxicity, significantly more patients suffered from neutropenia and infection in the AT-arm than in the AC-arm.

Another trial [22] compared docetaxel/doxorubicin/cyclophosphamide (TAC) with 5-FU/epirubicin/cyclophosphamide (FAC) as first-line treatment for metastatic breast cancer. In accordance with the previous study, TAC produced significantly higher response rates than FAC (54% vs 43 %, p = 0.023). So far, TTP and survival data are not available.

A third trial [23] compared the less cardiotoxic epirubicin/docetaxel (E75/T75) with FE75C. The patients eligible for this study had a recurrence-free interval of at

Table 1. — *Overview of objective response rate (ORR), time to progression (TTP) and overall survival (OS) of different chemotherapies in metastatic breast cancer.*

Agent		ORR (%)	TTP (weeks)	OS (months)
Alkylating agents		50-60	27-41	15-18
Anthracyclines	Mono	35-50		
	Poly	50-80	36-68	17-25
Docetaxel	1st line	40-68	31	7
	A-resistant	30-57	19	11
Paclitaxel	1st line	32-62	27	16.5
	A-resistant	6-48	19	11.7 (2nd line)
Vinorelbine	1st line	35-53		
	2nd line	15-47	12	8

Table 2. — *Monotherapy of taxanes versus monotherapy of anthracyclines in the first-line therapy of metastatic breast cancer.*

Author	Regimens	n	ORR (%)	TTP (months)	OS (months)
Sledge [15]	$P_{175\ mg/m^2/24h}$	245	33	5.9	19.9
	$A_{60\ mg/m^2}$	248	34	6.2	23.1
	$A_{50mg/m^2}\ P_{150\ mg/m^2/24h}$	246	46	8.0	22.2
Paridaens [14]	$P_{200\ mg/m^2}$	166	25	3.9	15.6
	$A_{75\ mg/m2}$	165	41	7.5	18.3
Chan [16]	$Doc_{100\ mg/m^2}$	161	48	6.5	15.0
	$A_{75\ mg/m^2}$	165	33	5.25	14.0

least 12 months after completion of the adjuvant treatment. Thus, the epirubicin dose was the same in both treatmemt arms. Response rates (63% vs 34%, $p < 0.05$) and TTP (7.8 months vs 5.9 months) were increased in the ET arm. But the survival data are not yet available. Taken together, all these three trials consistently demonstrate improved response rates and TTP with docetaxel/anthracycline combinations without showing clear evidence of a survival advantage.

Jassem *et al.* [24] compared in a phase III trial the efficacy and safety of doxorubicin and paclitaxel (A50 followed by Pac220/3h 24 hours later) with 5-FU/doxorubicin/cyclophosphamide (F500 A50 C500) as first-line therapy for women with metastatic breast cancer. Overall response rates for patients in the APac-arm and in the FAC-arm were 68% and 55%, respectively ($p = 0.032$). Median time to progression and overall survival were significantly longer for APac compared with FAC (TTP: 8.3 months vs 6.2 months, $p = 0.034$; OS: 23.3 months vs 18.3 months, $p = 0.013$); 24% of the patients primarily treated with FAC received a taxane as subsequent salvage therapy. Grade 3 or 4 neutropenias as well as grade 3 or 4 arthralgia and myalgia, peripheral neuropathy and diarrhea were more common with APac than with FAC, while nausea and vomiting were more common with FAC. The improved overall survival in the A followed by Pac treatment arm is unique among the trials listed in this review and might be caused by the application schedule with regard to the pharmakokinetic interaction between doxorubicin and paclitaxel and the resulting increased cardiac toxicity as well as the subsequent reduced doxorubicin cumulative dose when paclitaxel is given in close temporal relationship to bolus doses of doxorubicin.

Biganzoli *et al.* [25] compared the efficacy and tolerability of the combination of doxorubicin and paclitaxel (A60 Pac175 3h) with a standard doxorubicin and cyclophosphamide (A60 C600). The relative dose-intensity and delivered cumulative dose of doxorubicin were lower in the APac arm. Median progression-free survival was six months in both treatment arms. Response rate was 58% versus 54%, and median overall survival was 20.6 months versus 20.5 months in the APac and AC arm, respectively. The APac combination was characterized by a higher incidence of febrile neutropenia, 32% versus 9% and in the AC arm, and of decrease in the left ventricular ejection fraction in 27% of APac patients versus 14% in the AC arm. With regard to these side-effects and the similar response rates in both treatment arms, there was no clinically relevant benefit for the paclitaxel-containing regimen.

Sledge *et al.* [15] compared in a three-armed trial the efficacy of the combination of doxorubicin and paclitaxel (A50 Pac150/24h) with monotherapies containing doxorubicin (60 mg/m²) or paclitaxel (1750 mg/m² 24h). So far, no final report has appeared with regard to detailed data on the toxicity and subgroup analysis. Without improving the long-term survival the combination therapy APac demonstrates significantly higher response rates with 46% versus 34% or 33% for monotherapies with A or Pac, respectively.

In the two-armed multicenter phase III trial conducted by Carmichael *et al.* [26] a combination of epirubicin/paclitaxel (E75 Pac200/3h) is compared with E75 C600. Consistent with the previous trial similar response rates were seen in both treatment arms (40% vs 37%).

Table 3. — *Overview of phase III-trials comparing taxane containing monotherapy with polychemotherapy in metastatic breast cancer.*

Author	Regimens	n (%)	ORR (months)	TTP (months)	OS
CMF-Failure					
Chan [16]	Doc 100	326	48	6.1	15.0
	A 75		33	4.9	14.0
			p = 0.008	*p = ns*	*p = ns*
Anthracycline failure					
Nabholtz [17]	Doc 100	392	30	4.5	11.4
	MMC 12 + VBL 6		12	2.6	8.7
			p < 0.0001	*p < 0.001*	*p = 0.001*
Sjöström [18]	Doc 100	283	42	6.3	10.4
	MTX 200 + 5-FU 600		21	3.0	11.1
			p < 0.0001	*p < 0.001*	*p = ns*
Bonneterre [19]	Doc 100	172	43	nr	nr
	Vin 25 + 5-FU 750 ci		39		
			p = ns		
Phase II Study					
Friedrich [20]	Doc 100	34	70	9.0	nr
	E 90 + C600		64	10.0	nr
			p = 0.044	*p = 0.78*	

Table 4. — *Randomized trials of paclitaxel or docetaxel-anthracycline combinations.*

Author	Regimens	n	ORR (%)	TTP (months)	Survival (months)
Docetaxel regimens					
Nabholtz [21]	A 50 + T 75 vs	429	59	8.7	nr
	A 60 + C 600		47	7.4	
			p = 0.009	*p = 0.015*	
Nabholtz [22]	T 75 + A 50 + C 500	484	55	nr	nr
	F 500 + A 50 + C 500		44		
			p = 0.02		
Bonneterre [23]	E 75 + T 75 vs	142	63	7.8	nr
	F 500 + E 75 + C 500		34	5.9	
			p < 0.05	*p = 0.05*	
Paclitaxel regimens					
Sledge [15]	Pac 175739	33	5.9	22.0	
	A 60	34	6.2	20.1	
	A 50 + Pac 150		46	8.0	22.4
			p = ns	*p < 0.05*	*p = ns*
Jassem [24]	A 50 + Pac 220	267	68	8.3	23.3
	F 500 + A 50 + C 500		55	6.2	18.3
			p = 0.03	*p = 0.03*	*p = 0.01*
Biganzoli [25]	A 60 + Pac 175	275	58	nr	nr
	A 60 + C 600		54		
			p = ns		
Luck [27]	E 60 + Pac 175	560	46	nr	nr
	E 60 + C 600		40		
			p = ns		
Carmichael [26]	E 75 + Pac 200	705	67	6.5	13.8
	E 75 + C 600		56	6.7	13.7
			p = ns	*p = ns*	*p = ns*

ns = not significant; nr = not reported.

Compared with the multicenter study of the AGO [27], the increase of the epirubicin and paclitaxel doses resulted in a significant increase of clinically relevant toxicity like infections (14% and 11%, respectively) without improving response rates.

The available data concerning taxane/anthracycline combinations provoke one question: is the combination therapy better than sequential use of single agents? Because of the lack of survival advantage of the combination regimens both strategies are reasonable. However in patients with poor prognosis like rapidly progressive visceral metastases docetaxel/anthracycline combinations have clearly demonstrated superior efficacy with regard to response rates.

Capecitabine

Capecitabine is a 5-FU pro-drug which is converted to 5-FU after three sequential enzymatic reactions. After oral application, capecitabine is hydrolyzed and deaminated in the liver, followed by thymidine dephosphorylation at the tumor site. O'Shaughnessy *et al.* [28] published the data of a phase III trial that compares capecitabine (2x1250 mg/m²/day)/docetaxel (75 mg/m²) to docetaxel (100 mg/m²). The authors demonstrated that the treatment with capecitabine/docetaxel resulted in a significantly superior efficacy in time to disease progression (6.1 months vs 4.2 months), overall survival (14.5 months vs 11.5 months) and objective tumor response rate (42% vs 30%) compared with docetaxel. However, gastrointestinal side-effects and hand-foot syndrome were more common with combination therapy, whereas myalgia, arthralgia, and neutropenic fever/sepsis were more common with single-agent docetaxel therapy. Thus, docetaxel/capecitabine is an important treatment option for women with anthracycline pretreated metastatic breast cancer.

Conclusions

Comparing the efficacy and toxicity of the two taxanes, docetaxel and paclitaxel, appears very difficult, because there are - so far - no data available allowing a direct comparison. While three of the studies showed higher response rates of the docetaxel regimens than the comparative treatment arms, 75% of the paclitaxel-regimens only demonstrated similar anti-tumor activity compared with anthracycline-containing treatment arm. However, Jassem *et al.* demonstrated a substantial overall survival benefit with the combination of doxorubicin followed by paclitaxel 24 hours later. Thus, the conclusions of this review appear to demonstrate a benefit for docetaxel in the first-line therapy of metastatic breast cancer when compared with paclitaxel, but there are several unsolved questions like the sequence and interval of application of doxorubicin and paclitaxel. Furthermore, looking at the details, the trials were heterogeneous with respect to the doses and schedules of the compounds applied in the various combinations.

In case of non-responsiveness to the combination therapy of taxanes and anthracyclines, monotherapy with vinorelbine, capecitabine, gemcitabine and trastuzumab appear to be effective.

Table 5. — *Randomized trials comparing different paclitaxel schedules.*

Author	Regimens	n	ORR (%)	TTP (months)	Median survival (months)
Nabholtz [29]	135 mg/m² (3h)	471	22	3.0	10.5
	175 mg/m² (3h)		29	4.2	11.7
			p = ns	*p = 0.02*	*p = ns*
Peretz [30]	175 mg/m² (3h)	521	29		nr
	175 mg/m² (24h)		31		nr
			p = ns		
Winer [31]	175 mg/m² (3h)	475	21	3.8	9.8
	210 mg/m² (3h)		28	4.1	11.8
	250 mg/m² (3h)		22	4.8	11.9
			p = ns	*p = 0.03*	*p = ns*
Smith [32]	250 mg/m² (3h)	563	44	6.3	21.1
	250 mg/m² (24h)		54	7.2	21.9
			p = 0.02	*p = ns*	*p = ns*
Holmes [33]	250 mg/m² (3h)	179	23	4.5	11.0
	140 mg/m² (24h)		29	7.5	10.0
			p = ns	*p = ns*	*p = ns*

In the future, new treatment modalities consisting of combining different theraeutic principles like chemotherapy and target-specific antibody therapy may improve the treatment schedules with the aim of reducing side-effects and optimizing efficacy.

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