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Review

Use and abuse of taxanes in the management of metastatic breast cancer

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Abstract

Taxanes are currently introduced early in the treatment of patients with metastatic breast cancer (MBC), both as single agents and in combination with anthracyclines. Two different patient populations exist: those with no or minimal prior anthracycline exposure and those who have failed previous anthracyclines. The data generated through phase III trials in first-line MBC therapy will be reviewed and their interpretation for routine clinical practice (use versus abuse) will be discussed. Ways of improving taxane-based treatment tailoring both in the pre- and postgenomic eras will be addressed.

1. Introduction

Despite more than three decades of research with combination chemotherapy (CT), metastatic breast cancer (MBC) remains essentially incurable and, after documentation of metastasis, the median survival time is approximately 2 years. Although MBC responses to first-line CT regimens are common, the median duration of response is generally short (approximately 9 months).

Since its introduction in the early 1970s, doxorubicin has been considered one of the most active cytotoxic agents in the treatment of breast cancer. However, the now-common use of an anthracycline in earlier stages of breast cancer (i.e. in the adjuvant setting) has increased the likelihood of anthracycline-resistant MBC. In this situation, and in cases of progression after first-line anthracycline-based CT, the taxanes became the current 'standard of care'. These antimicrotubule agents (paclitaxel and docetaxel) have an innovative mechanism of action, which is p53-independent [1,2], and have now been evaluated in clinical trials for more than a decade. In fact, taxanes are currently introduced early in MBC treatment, in patients with no or minimal prior anthracycline exposure and/or in combination with anthracyclines. Furthermore, their role in the adjuvant setting is being investigated in numerous clinical trials involving 56 000 women.

This article will focus on the role of taxanes in the treatment of MBC: the existing phase III data regarding paclitaxel and docetaxel, administered alone or in combination, will be reviewed, their interpretation for routine clinical practice will be discussed (use versus abuse) and potential ways of improving taxane-based CT tailoring will be presented. The specific management of HER-2 overexpressing disease will not be discussed.

2. The taxane phase III data in metastatic breast cancer

The following section will describe the randomised phase III trials that evaluated the role of the taxanes in MBC. These trials have been classified according to previous anthracycline exposure of their patient population and according to the drug used, docetaxel or paclitaxel.

2.1. Minimal or no previous anthracycline exposure (Table 1)

2.1.1. Docetaxel

Three randomised phase III trials evaluated the role of docetaxel in this patient population, all as first-line therapy for MBC, one as monotherapy [3] and the two other as anthracycline-based combinations [4–6].

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2.1.1.1. Docetaxel—single agent. Docetaxel monotherapy was compared with doxorubicin monotherapy in 326 anthracycline-naïve patients, who had previously received alkylating agent-containing CT. Of the 326 patients randomised, 174 had received previous CT for MBC. The primary endpoint was time to progression (TTP). In an intent-to-treat analysis, docetaxel yielded a significantly higher overall response rate (ORR) ($P=0.008$), but the median TTP ($P=0.45$) and median overall survival (OS) ($P=0.39$) were not statistically different. Although crossover was not part of the study design, 28% of docetaxel-treated patients received anthracycline-based CT and 26% of anthracycline-treated patients received a taxane-based regimen as first treatment after study therapy. When adjusted for crossover treatment, the difference in OS between the two treatment arms remained non-significant. The median relative dose intensity (RDI) was 97% for docetaxel and 95% for doxorubicin. The percentages of withdrawals (54% versus 66%, $P=0.027$) and of delayed cycles (7% versus 15%) were lower in the docetaxel arm, while dose reductions occurred in a similar number of cycles (5% in both arms). The incidence of toxic deaths was higher in the anthracycline group (3%, mainly due to cardiotoxicity) than in the docetaxel group (1.2%). Grade 4 neutropenia was similar in both groups, but the incidence of severe neutropenic complications was higher with doxorubicin treatment. Non-haematological toxicity was reflective of the expected profile of each drug (i.e. cardiotoxicity, nausea/vomiting and stomatitis were more frequent with doxorubicin, whereas fluid retention, diarrhoea, skin toxicity, allergy, nail disorder and neurotoxicity occurred more commonly with docetaxel). Although there were limitations in the quality of life (QoL) assessment due to missing data, no major differences were seen between the two arms [3].

2.1.1.2. Docetaxel in combination. Used in combination with anthracyclines, docetaxel has shown an improvement

Table 1
Randomised phase III trials of taxanes in metastatic breast cancer with minimal or no previous anthracycline exposure

Study	No. pts	Treatment	RR (*P* value)	TTP (*P* value)	OS (*P* value)	Crossover	Conclusion
Single-agent							
Chan 1999 [3]	Total: 326	D	47.8%	26 w	15 m	Allowed.	D > A
	2nd-line: 174	A	33.3% (0.008)	21 w	14 m	28 and 26%, respectively.	(RR)
Bishop 1999 [7]	209	P	29%	5.3 m	17.3 m	No. at progression, epirubicin recommended.	P > > CMFp
		CMFp	35% (0.37)	6.4 m (0.25)	13.9 m (0.068)		(OS)
Paridaens 2000 [8]	331	P	25%	4.2 m	15.6 m	Early (76 versus 75%) or delayed (46 versus 65%) as per study design.	A < P
		A	41% (0.003)	7.5 m (<0.001)	18.3 m (0.38)		A = P < AP
Sledge 2003 [9]	739	P	34%	6.0 m	22.2 m	Allowed.	(RR, TTP)
		A	36%	5.8 m	18.9 m	Part of study design.	
		AP	47% (<0.007)	8.0 m (<0.009)	22.0 m		
Combination							
Nabholtz 1999 [4]	429	AD	60%	37.1 w	NA	NA	AD > AC
		AC	47% (0.012)	31.9 w (0.015)			(RR, TTP)
Mackey 2002 [6]	484	DAC	55%	31 w	21 m	D poststudy given to 11% of DAC and 38% of FAC	DAC > FAC (RR)
		FAC	44% (0.023)	29 w (0.51)	22 m (0.93)		
Jassem 2001 [10]	267	AP	68%	8.3 m	23.3 m	Not part of the design, but P poststudy given to 10% of FAC.	AP > > AC
		FAC	55% (0.032)	6.2 m (0.034)	18.3 m (0.013)		(OS)
Biganzoli 2002 [11]	275	AP	58%	5.9 m	20.6 m	Allowed, but not part of study design.	AP = AC
		AC	54% (0.51)	6.0 m (0.69)	20.5 m (0.49)		
Luck 2000 [12]	560	EP	46%	39 w	NA	NA	EP = EC
		EC	41%	33 w (0.089)			
Carmichael 2001 [13]	705	EP	67%	6.5 m	13.7 m	NA	EP = EC
		EC	56%	6.7 m (0.72)	13.8 m (0.92)		

D, docetaxel; P, paclitaxel; A, doxorubicin; C, cyclophosphamide; M, methotrexate; F, 5-fluorouracil; E, epirubicin; NA, not available; w, weeks; m, months; pts, patients; RR, relative risk; TTP, time to progression; OS, overall survival.

in terms of response rate (RR) in two trials [4–6] and in terms of TTP in one [4].

At the 1999 Annual Meeting of the American Association of Clinical Oncology (ASCO), Nabholtz and colleagues presented a randomised phase III trial comparing the combination doxorubicin and docetaxel (AD) to the standard combination doxorubicin and cyclophosphamide (AC), as first-line CT for 429 MBC patients. The patients were anthracycline-naïve, but had received adjuvant CT in 42% of cases. AD showed a significantly higher RR than AC (60% versus 47%, $P=0.0012$), and a longer TTP (37.1 versus 31.9 weeks, $P=0.015$). The median RDI was 96% for both arms and discontinuation due to toxicity occurred in 15% of cases in the AD arm and in 14% in the AC arm. Neutropenia was higher with AD (82% versus 69%, with fever in 6% versus 2%), but did not compromise the RDI. The incidence of cardiotoxicity was slightly higher in the AC arm (clinical congestive heart failure (CHF) 2% versus 4%; LVEF decrease $\geqslant$30 points 2 versus 5%), but no greater than that expected for the cumulative dose of doxorubicin. There were four toxic deaths, one in the AD arm (0.4%, non-septic) and three in the AC arm (1.4%, 1 septic) [4].

Two years later, the same group presented the first results of another randomised phase III trial comparing a three-drug combination regimen of docetaxel, doxorubicin and cyclophosphamide (DAC) to the standard American three-drug combination FAC (5-fluorouracil, doxorubicin and cyclophosphamide), as first-line CT in 484 MBC patients [5]. Prior adjuvant CT was allowed and had been given to 39% of patients (11% with anthracycline, but with a cumulative dose <240 mg/m^2). The results of this trial were updated at the 2002 ASCO meeting [6] and confirmed the superiority of DAC over FAC in terms of the RR (55% versus 44%, $P=0.023$), in an intent-to-treat analysis. However, no difference was observed in terms of the TTP (31 versus 29 weeks, $P=0.51$) or OS (21 versus 22 months, $P=0.93$). Post-study docetaxel was given to 11 and 38% of the DAC and FAC patients, respectively. The median RDI was 96% for DAC and 95% for FAC, while discontinuation due to toxicity occurred in 17% of cases in the DAC arm and in 8% in the FAC arm. Grade 3/4 events were more frequent with DAC, both haematological (neutropenia 94% versus 81%; febrile neutropenia 29% versus 5%) and non-haematological (stomatitis 8% versus 3%; diarrhoea 5% versus 1%). Cardiotoxicity was slightly higher with DAC (clinical CHF 2.4% versus 0.4%; LVEF decrease $\geqslant$30 points 4% versus 3%). There were seven toxic deaths, four in the DAC arm (2%, two septic) and three in the FAC arm (1%, three septic) [6].

2.1.2. Paclitaxel

2.1.2.1. Paclitaxel monotherapy. Three trials evaluated the role of paclitaxel monotherapy as first-line CT for MBC in a patient population with minimal or no anthracycline exposure. Unfortunately, their results are conflicting [7–9].

Bishop and colleagues compared paclitaxel as a single agent (200 mg/m^2 given as 3-h infusion) to a non-anthracycline combination CT (CMFP), in 209 patients with essentially previously untreated MBC. Some patients (21% versus 33%) had received prior adjuvant CT. No crossover was allowed, and patients whose disease progressed were recommended to receive epirubicin. In an intent-to-treat analysis, the ORR was slightly higher, although not significant, in the combination arm (29% versus 35%; $P=0.37$), and there was no significant difference between the treatment arms regarding the median TTP (5.3 versus 6.4 months; $P=0.25$). However, paclitaxel was associated with a significantly improved OS (17.3 versus 13.9 months, $P=0.068$). Dose reductions of more than 5% occurred in 23% of paclitaxel-treated patients and 32% of the CMFP patients. Nine percent of paclitaxel patients had a delay of $\geqslant$1 week, whereas 34% of CMFP patients experienced a similar delay. No data were available on the median RDI. Leucopenia, thrombocytopenia and mucositis were all significantly less severe with paclitaxel (all $P<0.001$), which also resulted in less febrile neutropenia and/or infection (10% versus 27%; $P=0.001$). Alopecia, peripheral neuropathy and myalgia/arthralgia were more severe with paclitaxel (all $P<0.0001$). Overall, QoL was similar for both treatments ($P\geqslant0.07$) [7].

In contrast, Paridaens and colleagues failed to prove the superiority of paclitaxel (175 mg/m^2 as a 3-h infusion) when compared with doxorubicin (75 mg/m^2 as a rapid infusion), in terms of RR and TTP, as first-line CT for 331 MBC patients [8]. The primary endpoints of this study were progression-free survival (PFS) in first-line CT and RR to second-line CT, while RR to first-line therapy, QoL and OS were secondary endpoints. Crossover was part of the study design for patients who progressed within the planned protocol courses ('early crossover') and a 'delayed crossover' was optional for all other patients at the time of disease progression. Prior adjuvant CT was administered in 32% of patients in the paclitaxel arm and in 33% of patients in the doxorubicin arm. In an intent-to-treat analysis, RR to first-line therapy was significantly better ($P=0.003$) for doxorubicin than for paclitaxel (41% versus 25%), with doxorubicin also achieving a longer median PFS (7.5 versus 3.9 months; $P<0.001$). For second-line therapy, RR was 30% with crossover to doxorubicin and 16% with crossover to paclitaxel, while the median survival durations were not significantly different (18.3 versus 15.6 months; $P=0.38$). Dose reductions and treatment delays were more frequent in the doxorubicin arm and, consequently, the average dose-intensity achieved with doxorubicin (93% of planned dose-intensity; range 53–103%) was lower than with paclitaxel (99% of planned

dose-intensity; range 72–107%). Median RDI in first-line therapy was 99% for paclitaxel and 93% for doxorubicin; in second-line therapy median RDI was 97% for paclitaxel and 92% for doxorubicin. Toxicities reflected the expected side-effects of each drug (more haematological, gastrointestinal and cardiac side-effects with doxorubicin, while neurotoxicity and arthralgia/myalgia were more common with paclitaxel). Six toxic deaths were encountered: three after doxorubicin in first-line therapy (two septic), two in second-line therapy (two myocardiopathies after a cumulative dose of 525 mg/m^2 of doxorubicin), and one after paclitaxel in second-line treatment (sepsis). Regarding cardiotoxicity, a total of 12 patients developed CHF, 6 patients (4%) on first-line doxorubicin, 2 on second-line paclitaxel, and 4 on second-line doxorubicin. In all of these patients, the median cumulative dose of doxorubicin was 480 mg/m^2 (range 300–675 mg/m^2). 29 patients (17 on first-line doxorubicin and 12 on second-line doxorubicin) ceased therapy because of a drop in LVEF of $\geqslant$20% of the baseline value. Myocardial ischaemic events were reported in an additional 3 patients (2 on doxorubicin and 1 on paclitaxel). A detailed QoL analysis showed that the greater toxicity of doxorubicin was compensated for by a better symptom control, particularly pain, compared with that achieved with paclitaxel [8].

The final results of the third study, a large phase III Intergroup trial (E1193), were recently published [9] and have shown equivalence between paclitaxel and doxorubicin. This trial compared doxorubicin, paclitaxel and the combination of doxorubicin and paclitaxel (with granulocyte colony-stimulating factor support) as first-line therapy for 739 MBC patients. Patients receiving single-agent doxorubicin or paclitaxel were scheduled by protocol to crossover to the other single-agent at time of disease progression. Around 30% of patients in each arm had received prior adjuvant CT. Objective responses were seen in 36% of patients receiving doxorubicin, 34% of those receiving paclitaxel and 47% of those receiving the combination ($P=0.77$ for doxorubicin versus paclitaxel, 0.017 for doxorubicin versus the combination and 0.006 for paclitaxel versus the combination). Median time to treatment failure (TTF) was longer for the combination arm (8.0 months) than for either single-agent doxorubicin (6.0 months) or single-agent paclitaxel (6.3 months) ($P=0.0022$ for doxorubicin versus the combination and 0.0567 for paclitaxel versus the combination). However, no significant difference in OS was seen, with a median survival of 19.1 months for doxorubicin, 22.5 months for paclitaxel, and 22.4 months for the combination ($P=0.60$ for doxorubicin versus paclitaxel; $P=0.82$ for doxorubicin versus the combination; $P=0.49$ for paclitaxel versus the combination). Responses were seen in 20% of patients crossing from doxorubicin to paclitaxel, and 22% of patients crossing from paclitaxel to doxorubicin. Grade 3/4 neutropenia was most common in patients treated with paclitaxel, while the incidence of infection and neutropenic fever was higher with the combination. Cardiac toxicity was equivalent in patients receiving single-agent doxorubicin and combination therapy. Lethal toxicities were rare in all of the groups and changes in global QoL were not statistically significant [9]. Of note, in this study, paclitaxel was given as a 24-h infusion at the dose of 175 mg/m^2.

2.1.2.2. Paclitaxel in combination. Four trials have evaluated the role of paclitaxel in combination regimens in this patient population and have also yielded conflicting results [10–13].

In 2001, Jassem and colleagues reported a phase III trial demonstrating the superiority of the combination doxorubicin and paclitaxel (where paclitaxel was administered 24 h after doxorubicin) over the standard FAC regimen [10], as first-line therapy in 267 MBC patients. TTP was the primary endpoint, and secondary endpoints were ORR, OS, toxicity and QoL. One prior non-anthracycline non-taxane-containing adjuvant CT regimen was allowed and received by 44 and 46% of patients in each arm, respectively. In an intent-to-treat analysis, median TTP (8.3 versus 6.2 months; $P=0.034$), OS (23.3 versus 18.3 months; $P=0.013$), and ORR (68 versus 55%; $P=0.032$) were significantly better for doxorubicin/paclitaxel compared with FAC. Patients treated with FAC received paclitaxel as second-line CT in 10% of cases and docetaxel in 14% of cases. Aside from the taxanes, other second-line agents were used in comparable frequency for patients treated on each of the study arms. Grade 3/4 neutropenia was more frequent with doxorubicin/paclitaxel than with FAC (89 versus 65%; $P<0.001$), but there was no difference in the incidence of febrile neutropenia (8 and 5% of patients, respectively; $P=0.339$). Non-haematological toxicities were generally reflective of the expected toxicity profiles of each of the regimens: grade 3/4 arthralgia and myalgia, peripheral neuropathy and diarrhoea were more common with doxorubicin/paclitaxel, whereas nausea and vomiting were more common with FAC. The incidence of cardiotoxicity was low and similar in both arms. There were two treatment-related deaths, one in each arm. Quality of life was also similar with the two regimens [10].

The European Organisation for the Research and Treatment of Cancer (EORTC) 10961 multicentre phase III trial, comparing the doxorubicin/paclitaxel combination to the standard doxorubicin/cyclophosphamide regimen, as first-line CT for 275 anthracycline-naïve MBC patients, was reported in 2002 [11]. The primary endpoint was PFS and secondary endpoints were RR, OS, safety and QoL. Prior adjuvant CT was given to 35 and 37% of patients, respectively. In an intent-to-treat analysis, no significant differences in the study endpoints were observed between the two treatment arms: median PFS was of 6 months in both groups ($P=0.65$), RR was 58

and 54% ($P=0.51$), and median OS was 20.6 and 20.5 months ($P=0.49$) in the doxorubicin/paclitaxel and doxorubicin/cyclophosphamide arms, respectively. The RDI and delivered cumulative dose of doxorubicin were lower in the doxorubicin/paclitaxel arm. Furthermore, treatment-related toxicity compromised the doxorubicin delivered dose-intensity in the paclitaxel-based regimen. Dose reduction or discontinuation was reported in 49 and 27% of the patients, respectively, while the percentage of treatment delays was similar in both arms. The incidence of grade 4 neutropenia was similar in the two treatment arms, but neutropenic fever occurred more frequently in patients treated with doxorubicin/paclitaxel (32 versus 9%, $P<0.001$). No major problems were encountered in terms of non-haematological toxicity, which was in accordance with the drugs expected side-effects profiles. LVEF decreases were documented in 27 and 14% of the patients, respectively, and CHF occurred in 3 patients in the doxorubicin/paclitaxel arm and in 1 patient in the doxorubicin/cyclophosphamide arm. There was one toxic death, caused by neutropenic sepsis, in this latter arm [11].

In two phase III trials, epirubicin was the selected anthracycline used in combination with paclitaxel and compared with the epirubicin/cyclophosphamide regimen, as first-line treatment for MBC patients. Despite a large sample size, results failed to show superiority of the paclitaxel-based regimens [12,13].

The first interim analysis of the AGO Breast Cancer Group study was reported at the 2000 ASCO meeting, and comprised the data from 429 of the 560 randomised patients, at a median follow-up of 36 weeks [12]. The combination of epirubicin/paclitaxel was as active as epirubicin/cyclophosphamide (ORR 46% versus 41%) and there was no significant difference in median PFS (39 versus 33 weeks, $P=0.089$). Neutropenia grade 3/4 was observed in 34 and in 45% of patients, respectively, while the incidence of febrile neutropenia was the same (2%) in both arms. 2 patients developed grade 3 cardiotoxicity, both in the paclitaxel-based arm. Final results of this trial are awaited.

The UK Coordinating Committee on Cancer Research (UKCCCR) ABO1 trial compared the same two regimens as first-line treatment of 705 MBC patients [13]. Prior adjuvant CT was administered to 54% of patients (anthracycline-based in 14%). Epirubicin dose intensity was equivalent in both arms. A greater proportion of paclitaxel-treated patients achieved objective remissions as best response to treatment (67% versus 56%). However, differences in terms of median PFS (6.5 versus 6.7 months, $P=0.72$) and median OS (13.7 versus 13.8 months, $P=0.92$) were not statistically significant. Excluding alopecia, 46 and 37% of patients, respectively, had grade 3/4 toxicities during treatment, with severe infection occurring in 14% of patients of the paclitaxel/epirubicin arm and in 11% of the epirubicin/cyclophosphamide arm. Severe mucositis ($P=0.02$) and neurotoxicity ($P=0.003$) were observed more frequently in the paclitaxel-treated patients. QoL during treatment was similar for both arms.

2.2. Previous anthracycline-exposure (anthracycline-resistance or failure) (Table 2)

There is a lack of paclitaxel-based phase III trials after anthracycline failure, with all existent four trials using docetaxel, three as monotherapy [14–16] and in one in association with capecitabine [17].

2.2.1. Docetaxel—single agent

In 1999, Nabholtz and colleagues published the results of a randomised phase III trial comparing docetaxel monotherapy to the combination mitomycin/vinblastine, in 392 MBC patients. All patients in both arms had progressed despite previous anthracycline-containing CT, given in the adjuvant setting (17 and 21%), the metastatic setting (49 and 50%) or both (34 and 29%) settings. Although crossover was not part of the study design, at the time of progression, 47% of docetaxel-treated patients received further CT (12% of which with mitomycin/vinblastine) and 54% of mitomycin/vinblastine-treated patients also received further CT (24% of which with docetaxel). The study primary endpoint was TTP. In an intent-to-treat analysis, docetaxel was significantly superior to the combination arm in terms of RR ($P<0.0001$), median TTP ($P=0.001$) and OS ($P=0.0097$). The latter remained significantly higher for docetaxel ($P=0.007$) when adjusted for crossover. The median RDI was 94% for docetaxel, 99% for mitomycin, and 97% for vinblastine. Both arms had similar proportions of treatment delay (9.9% versus 9.3%) and similar withdrawal rates (11.8% versus 6.9%), but dose reductions were more common with docetaxel (19.7% versus 4%). The incidence of febrile neutropenia (9% versus 0.5%), grade 3/4 infections (11% versus 1.1%) and grade 3/4 neutropenia (93% versus 62%) were significantly higher in the docetaxel-treated group, as were most non-haematological adverse events such as stomatitis (9.0% versus 0.5%), diarrhoea (7.5% versus 0%), skin toxicity (4.0% versus 0%), asthenia (16% versus 6.4%), neurotoxicity (5% versus 0.5%) and nail disorders (2.5% versus 0%). Conversely, grade 3/4 thrombocytopenia (12% versus 4%) and constipation (0.5% versus 3.2%) were significantly more frequent in the mitomycin/vinblastine arm. Toxic deaths (2% versus 1.6%) and the QoL analysis were similar in both arms [14].

The Scandinavian Breast Group conducted a randomised phase III trial comparing docetaxel with sequential methotrexate/5-fluorouracil, in 283 MBC patients after anthracycline failure [15]. After progression, crossover to the alternative treatment group was recommended.

The efficacy analyses were done according to the intention-to-treat principle and the study primary endpoint was TTP, while RR, toxicity and QoL were secondary endpoints. Docetaxel produced a significantly higher ORR (42 versus 21%, $P<0.001$), which remained superior after crossover (27% versus 12%), and a better median TTP (6.3 versus 3 months, $P<0.001$). Median OS, including the crossover phase, was not statistically different in both arms (10.4 versus 11.1 months, $P=0.79$). The median relative given dose per course (99% in both arms) and the median RDI (95% versus 94%) were similar in both arms, as were the percentages of treatment withdrawals (94% versus 95%). Overall treatments were well tolerated with infrequent grade 3/4 toxicities in both arms, with the exception of fatigue, alopecia and infections. Most side-effects (including leucopenia, febrile neutropenia, infection, oedema, peripheral neuropathy, asthenia, nail changes, skin toxicity, stomatitis, alopecia, allergy and diarrhoea) were more frequent in the docetaxel arm, while conjunctivitis occurred significantly more in the combination arm. There were three toxic deaths in the docetaxel arm and one in the methotrexate/5-fluorouracil arm. Nevertheless, QoL evaluation concluded that differences between the two arms were minor [15].

Finally, in 2002 the final results of the French study, comparing docetaxel with the combination of 5-fluorouracil/vinorelbine in 176 patients with MBC, were published [16]. All patients had failed anthracycline-based CT given as neo-adjuvant or first-line metastatic treatment. The study primary endpoint was TTP and secondary endpoints were RR and OS. At a median follow-up of 30.3 months, median TTP (6.5 versus 5.1 months), ORR (43% versus 38.9%, $P=0.69$) and OS (16 versus 15 months) did not differ significantly between the two arms. Dose reductions (17% versus 44%) and treatment delays (3.9% versus 25%) were significantly more frequent in the combination arm and, consequently, the RDI of docetaxel was 97%, while those of 5-fluorouracil and vinorelbine were 88 and 84%, respectively. The main toxicity in both treatment arms was neutropenia. Grade 3/4 neutropenia was significantly more frequent with docetaxel (82% versus 67%; $P=0.02$), while severe thrombocytopenia (10% versus 1%; $P=0.02$) and severe stomatitis (40% versus 5%; $P<0.0001$) were significantly more frequent with the combination. Febrile neutropenia (22% versus 13%; $P=0.10$) and grade 3/4 infection (7% versus 2%; $P=0.28$) also occurred more frequently with 5-fluorouracil/vinorelbine. In contrast, docetaxel led to more alopecia (67% versus 24%; $P<0.0001$) and grade 1/2 sensory neuropathy (35% versus 6%; $P<0.0001$). There were six treatment-related deaths, one in the docetaxel arm and five (three septic) in the combination arm [16].

2.2.2. Docetaxel in combination

So far, only one phase III trial compared docetaxel as monotherapy versus docetaxel in combination with capecitabine [17] and yielded superior results in terms of OS with the combination, in 511 MBC patients, resistant or relapsing after anthracycline-based therapy. The majority of patients in both arms (65 and 67%) received the study drugs as 2nd- or 3rd-line CT. Prior anthracycline-based CT was administered in 42% of patients in both arms, either in the (neo)adjuvant or metastatic setting. The primary endpoint was TTP and secondary endpoints were RR, OS and QoL. Crossover was not part of the study design; however, 20% of patients from the combination arm received single-agent docetaxel as poststudy CT, and 17% of patients from the monotherapy arm received single-agent capecitabine after study. In an intent-to-treat analysis, the combination arm was significantly superior in terms of TTP (6.1 versus 4.2 months, $P=0.0001$), OS (14.5 versus 11.5

Table 2
Randomised phase III trials of taxanes in metastatic breast cancer after anthracycline failure

Study	No. pts	Treatments	RR (*P* value)	TTP (*P* value)	OS (*P* value)	Crossover	Conclusion
Single-agent							
Nabholtz 1999 [14]	392	D	30%	19 w	11.4 m	Allowed.	D > > Mito + VBL
		Mito + VBL	11% (<0.0001)	11 w (0.001)	8.7 m (0.0097)	12 and 24%, respectively.	(OS)
Sjostrom 1999 [15]	283	D	42%	6.3 m	10.4 m	Recommended.	D > M→F
		M→F	21% (<0.001)	3.0 m (<0.001)	11.1 m (0.79)	18 and 28%, respectively.	(RR, TTP)
Bonneterre 2002 [16]	176	D	43%	6.5 m	16 m	NA	D = FUN
		FUN	38.8% (0.69)	5.1 m	15 m		
Combination							
O'Shaugnessy 2002 [17]	511	D + Cape	41.6%	6.1 m	14.5 m	Not part of study design, but Cape poststudy to 15% of D.	D + Cape > D
	⩾2nd-line: 340	D	29.7% (0.006)	4.2 m (0.0001)	11.5 m (0.0126)		(OS)

D, docetaxel; Mito, mitomycin; VBL, vinblastine; M, methotrexate; F, 5-fluorouracil; N, vinorelbine; Cape, capecitabine; NA, not available; w, weeks; m, months; FUN, 5-fluorouracil and vinorelbine.

months, $P = 0.0126$), and objective RR (42% versus 0%, $P = 0.006$). In the combination arm, the median delivered dose of capecitabine during the course of the study was 77% of the planned dose, and the corresponding value for docetaxel was 87%. In the single-agent docetaxel arm, the overall median delivered dose was 100% of the planned dose and the median delivered versus planned dose was 100% up to week 27 and was 75% in weeks 28–30. Approximately two-thirds of patients (65%) in the combination arm required a dose reduction of capecitabine alone (4%), docetaxel alone (10%), or both drugs (51%) for adverse events, while in the docetaxel single-agent arm, 36% of patients required a dose reduction. Premature withdrawal for adverse events or intercurrent illness was slightly more common in the combination arm than in the docetaxel arm (26% versus 20%). Gastrointestinal side-effects and hand–foot syndrome were more common with the combination therapy, whereas myalgia, arthralgia, and neutropenic fever/sepsis were more common with single-agent docetaxel. More grade 3 adverse events occurred with combination therapy (71% versus 49%), whereas there was a slightly lower incidence of grade 4 side-effects with the combination therapy (25% versus 31%). There were four toxic deaths, three (1.2%) in the combination arm and one (0.4%) in the single-agent arm. Overall, there were no significant differences regarding QoL [18].

3. Critical interpretation for routine clinical practice

3.1. Critical review of the existing randomised phase III trials

In order to optimise the use of taxanes as first-line therapy for MBC in daily clinical practice, a critical review of all the existing data is required, tackling important issues such as the benefit/risk ratio, the best taxane and optimal drug administration in terms of dose and schedule, and the identification of the subsets of patients most likely to benefit from these drugs.

3.1.1. Efficacy

For the patient population with *minimal or no previous anthracycline exposure*, the only possible conclusion, at the present time, is that no new standard of care' exists! This is a direct consequence of the fragmentation of breast cancer research in this area, with most of the trials being of relatively small sample size (only two studies enrolled more than 500 patients) [9,13] and therefore underpowered to detect small, but real, differences between treatment arms. Another important limitation is the absence of a built-in or allowed crossover in many of these trials, which would more accurately reflect routine clinical practice, where MBC patients are treated sequentially with different CT regimens at disease progression. Furthermore, only one trial [9] addressed the important question of use of taxanes as single agents versus in combination. Taking together the docetaxel efficacy data, in this population, shows that this drug yielded improved RR in all of the trials and improved TTP in most of them. However, these advantages did not translate into any survival benefit. For paclitaxel, the randomised trials generated conflicting results in terms of RR and TTP which, however, translated into a survival benefit in two of the studies.

For the patient population *previously failing anthracycline-based CT*, there are no published trials evaluating the role of paclitaxel as opposed to docetaxel, which was used in the four existing studies [14–17]. Unfortunately, all these trials are underpowered (only one has a sample size of 511 patients) [17] and in none of them is crossover a part of the study design. Notwithstanding these limitations, these four trials provide highly consistent results, with the use of docetaxel, in monotherapy or in combination with capecitabine, resulting in an improved RR, TTP and, most importantly, a survival advantage in two of the trials [14,17]. It can therefore be concluded that sufficient data supports the use of docetaxel for MBC after anthracycline failure as the new 'standard of care'; systematic use of the docetaxel–capecitabine combination is debatable, given the substantial toxicity and the lack of a proper comparison with the sequential use of the two agents. In the view of the authors, this regimen is most attractive in 'emergency' situations in which a rapid response is warranted.

3.1.2. Toxicity (Fig. 1)

In both patient populations, overall toxicity of combination CT is higher than the one of single-agent regimens. When used as monotherapy in first-line MBC and compared with taxanes, anthracyclines produce more febrile neutropenia (12% versus 6 or 7% for paclitaxel

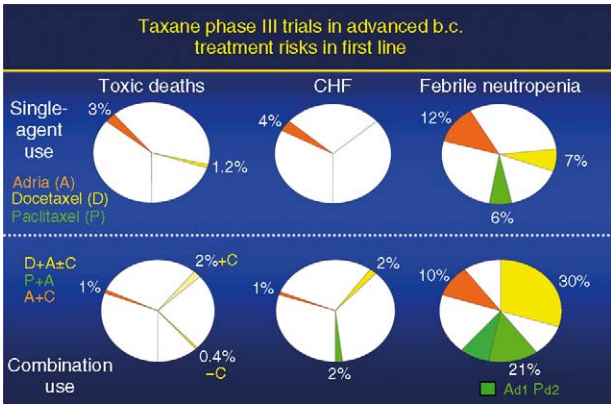

Fig. 1. Comparative treatment risks of taxanes used as first-line CT for MBC. Adria, doxorubicin; MBC, metastatic breast cancer; CT, chemotherapy; CHF, congestive heart failure; b.c., breast cancer.

and docetaxel, respectively), more toxic deaths (3% versus a negligible percent with paclitaxel, and 1.2% with docetaxel), and more cardiotoxicity (4%).

3.1.3. Preferred taxane

In the case of minimal or no anthracycline exposure, 1605 patients were treated in phase III trials with a taxane single–agent, 80% of which with paclitaxel, and 3459 patients with a taxane-based combination regimen, 74% of which paclitaxel-based. After anthracycline failure, a total of 1362 patients received a docetaxel-based regimen as first-line CT for MBC in a phase III trial, 511 of which as a single agent. As mentioned above, there are no phase III trials with paclitaxel-based CT in this population.

Since no 'head-to-head' direct comparison between docetaxel and paclitaxel has been published, the choice between the two drugs must rely on indirect comparisons, bulk and quality of existing data for each drug in each setting and differences in toxicity profiles, which may be of great importance for certain patients. An important factor to be taken into consideration when choosing an anthracycline–taxane combination regimen is the difference in pharmacokinetic interactions between docetaxel or paclitaxel and doxorubicin. While docetaxel does not alter the area under the curve (AUC) of anthracyclines [18,19], paclitaxel increases the AUC of doxorubicin and doxorubicinol, its cardiotoxic metabolite [20,21]. This pharmacokinetic interaction is thought to be the reason for the high RR (83–94%), but also for the high rates of CHF (18–20%) seen in the early trials of the paclitaxel–doxorubicin combination [22,23]. Since then several strategies have been used to try to maintain the efficacy of the combination while minimising the cardiotoxicity risk, including: (a) longer infusion times (i.e. 24 h) for paclitaxel; (b) longer time interval between the doxorubicin and paclitaxel administrations; (c) limitation of the cumulative doxorubicin dose to 360 mg/m^2; and (d) use of epirubicin instead of doxorubicin and of docetaxel instead of paclitaxel [24].

There is, however, one study directly comparing the two taxanes, sponsored by Aventis, that has recently closed its accrual and preliminary results are expected to be presented this year.

3.1.4. Drug administration

For both taxanes, there are two main schedules of administration, weekly and 3-weekly, each having some weaknesses and advantages. The weekly schedule has not yet been evaluated in randomised phase III trials (several phase II trials have been published) and carries the obvious inconvenience of requiring weekly visits to the hospital/clinic for the drug administration. However, this regimen also provides some important differences in the toxicity profile of both paclitaxel and docetaxel, namely myelosupression is substantially reduced. In particular, weekly paclitaxel (80 mg/m^2/week) is generally very well tolerated, with manageable neurotoxicity and rare febrile neutropenia, making it one of the preferred regimens in the metastatic setting. Adding to these advantages, studies in the neoadjuvant setting have raised the possibility of a superior efficacy for this regimen [25]. Several factors may contribute to this potential superiority [26]: (a) a more sustained exposure of dividing tumour cells to the cytotoxic effects of paclitaxel by administering it on a weekly basis; (b) greater inhibition of tumour regrowth between cycles (dose-dense principle); (c) improved paclitaxel therapeutic index; (d) decrease probability of emergence of resistant malignant cell subpopulations; and (e) enhanced apoptotic [27] and antiangiogenic effects of paclitaxel when given weekly. Weekly docetaxel (30–35 mg/m^2/week) may be equally effective, although less well tolerated, especially in terms of fatigue.

The 3-weekly schedule has been extensively studied in both taxanes. However, unlike docetaxel where a general consensus exists regarding the best dose and infusion time to use (100 mg/m^2 in 1 h), the optimal dose and schedule of paclitaxel are yet to be defined. Several prospective studies, enrolling a total of 1688 patients, have evaluated different variants of the paclitaxel 3-weekly schedule: different doses (ranging from 135 to 250 mg/m^2) and different infusion times (ranging from 3 to 96 h) have been tested [28–31]. Longer infusion times, such as 24 or 96 h, have not been found superior to a 3-h infusion [32] and it now seems to be generally accepted that single-agent paclitaxel should be administered at a dose of 175 mg/m^2 during a 3-h infusion.

Since there is only partial cross-resistance between the two taxanes, their sequential use is possible, in particular for patients who are initially taxane-sensitive [33–36].

3.1.5. Selection of patients

Randomised clinical trials and meta-analyses have been our best tools so far for understanding which therapies provide a sustained survival benefit, and what the magnitude of this benefit is *on average*. However, this 'traditional' approach of comparing treatment A versus treatment B extrapolates to the individual conclusions of studies carried out in a population. This inevitably leads to the inefficient treatment of many, in order to benefit a few, and possibly to excessive toxicity in certain specific groups of patients. Our large randomised clinical trials, run in patients unselected for their tumour biological characteristics, tell us that, *on average*, treatment A is superior to treatment B, a result that will guide, across the board, treatment for future patients (i.e. all future patients will receive treatment A). However, in a very heterogeneous disease such as breast cancer, this global treatment effect 'A is better than B', is in reality highly likely to reflect different scenarios: (a) all subpopulations derive a benefit; (b) one subpopulation

derives a benefit and another a negligible one; or, (c) one subpopulation derives a large benefit and another has, in fact, a detrimental effect (A < B). Such heterogeneity in treatment effects is clearly exemplified by the different efficacy of certain chemotherapy regimens in endocrine-non-responsive and endocrine-responsive breast cancers. Therefore, the identification of the subset(s) of patients most likely to benefit from each drug is crucial, particularly in the case of very active, but also expensive and toxic, agents such as the taxanes.

In the pregenomic era two approaches were mainly used to better understand which patients can derive the most benefit from these drugs: (1) subset analysis in the randomised phase III trials, and (2) biological markers studies.

Subset analysis, with all its limitations, can provide us with some hints on this subject, especially if the results are consistent throughout the trials. Some patients' characteristics are associated with a better response to taxanes, when compared with anthracyclines, namely visceral metastasis in particular liver involvement and a disease-free interval (DFI) inferior to 12 months.

Several biological markers studies have been performed in the metastatic setting. Unfortunately, all of them were retrospective and underpowered to provide any definite conclusions. Additional limiting issues are the quality of collected tumour tissue and the lack of standardisation and high levels of inter-laboratory variability in the immunohistochemistry (IHC) technique, commonly used to evaluated most biological markers. Despite these limitations, these studies give us valuable insights and generate interesting hypotheses regarding the potential correlation between response to therapy and certain biological characteristics of breast cancer.

Three of the randomised phase III trials [3,8,15] described in the previous section had companion studies done retrospectively. In the EORTC trial, comparing single-agent paclitaxel to single agent doxorubicin, p53, HER-2, and bcl-2 were evaluated and correlated with the response to therapy. No significant association was found [37]. Sjostrom and colleagues evaluated several markers by IHC, including HER-2, p53, mdm-2, p21 and MIB-1, but none of them was able to predict response to docetaxel [38]. The role of HER-2 and topoisomerase II alpha by fluorescent *in-situ* hybridisation (FISH), oestrogen receptor and microtubule-associated parameters (alpha and beta tubulin, beta tubulin isotypes, tau protein) by IHC as predictive markers was evaluated in the TAX 303 trial [3], which compared single agents docetaxel and doxorubicin; although no statistical significant correlation was found, the results suggested that in HER-2-positive MBC patients docetaxel might be more effective than doxorubicin, while the two treatments probably have a similar efficacy in HER-2-negative patients [39]. From a biological point of view, the most attractive potential predictive markers for taxane-based therapy are the microtubule-associated parameters (MTAP), since they are their specific targets. A pilot study conducted at the Jules Bordet Institute has shown that the tau protein and the class II β-tubulin isotype seem to be the most promising markers among the MTAP family [40]. However, these results need to be confirmed.

Due to the limitations already discussed, to date there is no marker that can accurately predict response to a taxane-based regimen and that can be routinely used. Large, prospective and biologically-based trials are needed and two such studies, the EORTC p53 and the TOP trial, are currently being conducted in the (neo)adjuvant setting.

3.2. *Influence of physician bias*

In view of the limitations of the data generated by the above-described phase III trials, it is not surprising that physician's bias strongly influences the prescription of the taxanes in advanced breast cancer in two ways: firstly, in the selection of a taxane versus a non-taxane-based CT for a given patient and, secondly, in the choice between a single agent taxane or a taxane combination.

The current heterogeneity in the selection of CT options is exemplified by the patient scenario illustrated in Fig. 2, which was distributed by the International Oncology Foundation to 556 oncologists worldwide. The preferred drug or regimen, illustrated in Fig. 3, greatly varied: approximately two-thirds of the physicians choosing a taxane-based combination and one-third a single-agent regimen (taxane or anthracycline). Therefore, one could say that the medical oncology community can be divided into two 'fields': one which favours combination regimens in all 'endocrine resistant'

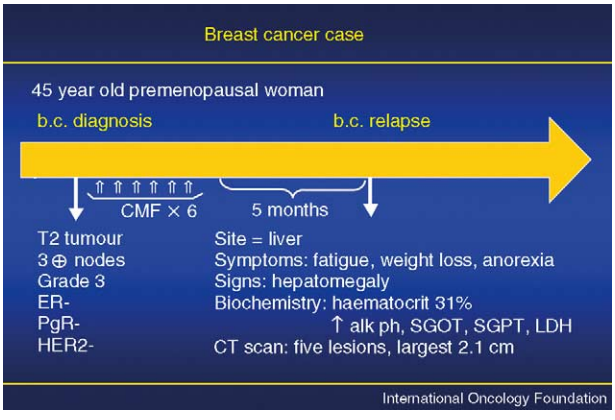

Fig. 2. Breast cancer clinical case presented by the International Oncology Foundation. CMF, cyclophosphamide; methotrexate, 5-fluorouracil; CT, computed tomography; alk ph, alkaline phosphatase; LDH, lactate dehydrogenase; ER, oestrogen receptor; PgR, progesterone receptor.

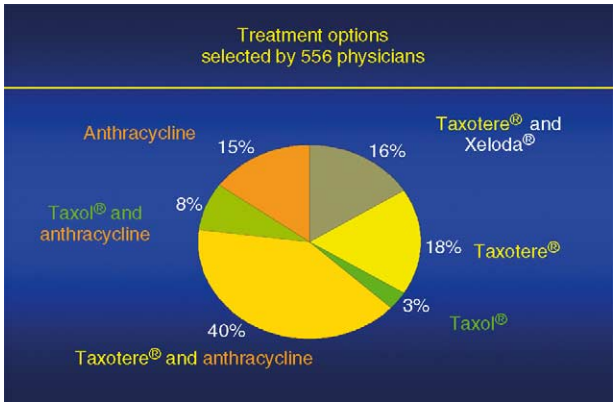

Fig. 3. Breast cancer clinical case presented by the International Oncology Foundation—Oncologists' treatment options. Taxol®, Paclitaxel; Taxotere®, Docetaxel; Xeloda®, Capecitabine.

patients, while the other uses single agents in sequence, unless there are symptoms or signs of life-threatening disease. Once the decision has been taken to offer a taxane, again physicians' bias will enter the equation of treatment decision-making: some oncologists always use combinations, while others prefer single-agent use, unless there is an emergency scenario. Of note, it is highly desirable that the patient's preference and comorbidities enter this equation as well.

4. Taxane-based chemotherapy tailoring—ways forward

In recent years, cancer research has been focusing on treatment individualisation or treatment 'tailoring' for each patient, aiming at optimising efficacy, improving QoL, reducing toxicity and healthcare costs.

When selecting the most appropriate medical therapy for the individual patient, several factors must be taken into consideration: (1) a careful evaluation of the risk of disease progression and the need for prompt symptom relief; (2) assessment of the balance between the treatment benefit and its associated risks; (3) the patient preference; (4) the overall cost of treatment and its complications; and (5) the biological characteristics of the tumour.

Two major efforts are being undertaken to address the need for predictive markers of response to taxanes and a better selection of patients most likely to benefit from these agents.

A joint meta-analysis project of all the randomised phase III trials evaluating docetaxel and paclitaxel as first-line treatment for MBC is being planned, with an independent statistical analysis coordinated by the International Institute for Drug Development. This meta-analysis will hopefully give the definite answer regarding the value of the taxanes when compared with anthracyclines, and the relative merit of taxane–anthracycline combination and sequential approaches. It will also try to identify the subset(s) of patients who derive the greater benefit from this therapy and potential surrogate markers for long-term survival.

The neoadjuvant setting represents an extraordinary resourceful setting to evaluate response to treatments and potential predictive markers. In this postgenomic era, the clinical application of new and evolving techniques such as DNA microarray and proteomics hold the promise of leading to the discovery of 'biological signatures' of both prognostic and predictive value. As a promising example, in a pilot study conducted at the Breast Medical Oncology Department of the MD Anderson Cancer Center, using c-DNA microarray technology, researchers were able to clearly separate the patients who achieved a complete pathological response to taxane-based CT (paclitaxel followed by FAC) given as preoperative systemic therapy, from those who did not achieve such response [41]. The top 100 markers that allow that distinction are currently being determined.

5. Conclusions

The optimal management of MBC remains a significant therapeutic challenge. The phase III data generated over the last decade have suffered from clinical trial design limitations and, consequently, did not provide us with a consensual new 'standard of care' for first-line MBC treatment. One exception may be the use of docetaxel in anthracycline-resistant disease, which many investigators now consider to be the 'reference drug' in this setting.

Currently, the routine clinical use of the taxanes is highly dependent on physicians' bias towards weighing their benefits and risks. Hopefully, in the near future this situation will change, when both the joint meta-analysis project and the ongoing translational research studies in the early disease setting will substantially contribute to improved taxane-treatment tailoring.

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