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INVITED COMMENTARY

Taxane vs. taxane: is the duel at an end? A commentary on a phase-III trial of doxorubicin and docetaxel versus doxorubicin and paclitaxel in metastatic breast cancer: results of the ERASME 3 study

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Abstract Taxanes (paclitaxel and docetaxel) comprise a class of mitotic inhibitors which considered highly active chemotherapeutic agents against cancer cells, and have become a cornerstone in the treatment of patients with early and advanced breast cancer. Following the initial generation of trials conducted to prove their efficacy, investigators turned to explore which taxane is superior in terms of efficacy, side effects, and quality of life based on head-to-head comparisons of paclitaxel versus docetaxel containing regimens. Moreover, many trials conducted to evaluate the optimal taxane dosing and schedule. This commentary discusses the ERASME 3 trial which compared the quality of life after four courses of doxorubicin combination with either paclitaxel or docetaxel, and also, it reviews all trials compared paclitaxel to docetaxel in both early and metastatic disease settings, in terms of efficacy, dosing, schedule, and toxicity profile.

Keywords Breast cancer · Chemotherapy · Taxane · Paclitaxel · Docetaxel · ERASME 3 study

Introduction

Taxanes are among the most successful chemotherapy agents used in the management of breast cancer. The taxanes exert their antitumor activity by binding tubulin and stabilizing nonfunctional microtubule bundles, thereby blocking normal mitotic spindle development and causing cell cycle arrest in G2 phase [1]. Although synthesis of paclitaxel and its analogue, docetaxel, first began in the late 1970s and early 1980s, clinical development of the taxanes for breast cancer treatment was flourished in the 1990s, when the antitumor activity of single-agent regimens in patients with advanced disease began to be documented in phase II trials [2–6]. Initially, the use of taxanes was limited by hypersensitivity reactions, but once these were better managed (largely by premedication with steroids), taxane use became more common. After it have showed efficacy in metastatic breast cancer, the taxanes are now vital component in the treatment of early-stage disease, in which their addition to adjuvant treatment of early breast cancer has been shown to improve overall survival. Combinations of taxanes with other chemotherapeutic agents and targeted therapies have further improved survival for both early and metastatic disease. New formulations of taxanes (ABI-007) may both improve antitumor activity and reduce toxicity [7, 8].

This commentary reviews the current status of taxane therapy of breast cancer; it discusses efficacy and tolerability of taxane monotherapy or combination therapy, in comparison with other standard regimens in both early and metastatic disease settings, in terms of overall response rate (ORR), time to progression (TTP), and overall survival (OS). Also, it addresses important clinical questions of optimal taxane dose and schedule, and the preferred taxane (based on head-to-head comparison).

The ERASME trial

The ERASME 3 trial [9] presented in this issue of Breast Cancer Research and Treatment is a randomized controlled

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trial comparing the combination of doxorubicin and paclitaxel (AP) with the combination of doxorubicin and docetaxel (AD) in the setting of front-line chemotherapy for metastatic breast cancer. The primary endpoint of the trial, somewhat unusually, is overall quality of life (QoL), or more specifically, quality of life measured at the single time point of four cycles of chemotherapy.

Why chose such a time-point, and why chose 4 cycles of therapy? QoL was chosen because, in the author's words "We hypothesized that AD and AP combinations would yield similar results in terms of ORR and PFS, but were likely to have different toxicity profiles and hence could derive different benefits in terms of QoL". But is this the case? A randomized controlled trial of docetaxel versus paclitaxel showed a significant overall survival advantage favoring docetaxel in front-line metastatic breast cancer (15.4 vs. 12.7 months, $P = 0.03$) [10], and, in an admittedly underpowered survival analysis performed in the Erasme trial, AP came close to beating AD (27.3 vs. 21.4 months, $P = 0.081$). Would a larger trial have shown a survival advantage? It is of course impossible to say.

Regarding QoL, 4 cycles represents a convenient time-point for measurement. Most of those fated to respond (and therefore benefit symptomatically) will have done so by this point, and few of those destined to progress on chemotherapy will have done so. Compliance (always a concern in QoL studies) remained good, and patients had not yet crossed over to single agent therapy.

So how did the regimens compare? In general terms, they were equivalent. This is not to say that the regimens had identical effects; real differences in toxicity exist. But QoL measurements are blunt instruments, and unable to provide evidence for subtle distinctions between the two chemotherapy regimens examined.

Why might this be the case? QoL is an amalgam of many things. These include therapeutic effects (shrinkage and drug toxicity), tumor-driven effects, host differences (both physical and psychological) and ultimately unmeasurable aspects of the human spirit. A chemotherapy regimen is only likely to improve QoL in a symptomatic patients who responds to chemotherapy (i.e., you can't make someone who is asymptomatic feel better by administering cytotoxic chemotherapy), and only then if not outweighed by toxic effects.

Taxanes in metastatic breast cancer (MBC)

The ERASME 3 trial represents part of a long duel in the breast cancer world. Taxanes have demonstrated efficacy in multiple large and high quality phase III trials in the metastatic setting, but is there a "best" taxane? And what do we even mean by "best"?

Paclitaxel

Paclitaxel monotherapy has significant activity in both Anthracycline-naive (ORR 35–55%) [11–13] and Anthracycline-refractory MBC (ORR consistently at least 20%) [2, 4, 11–16]. Response rates obtained in randomized controlled trials has—as is not unusual in the breast cancer field—resulted in lower response rates than in the initial Phase II trials.

Dose and schedule

The original "standard" dose of paclitaxel was 175 mg/m^2 over 3 h every 3 weeks; a lower dose (135 mg/m^2) [17] has inferior efficacy, and higher doses (210 and 250 mg/m^2) did not improve response rate, survival, or quality of life in CALBG 9342 [18]. Although higher dose therapy was associated with a slight improvement of TTP, it was offset by higher toxicity [18, 19]. Continuous 24-h infusion of paclitaxel, results in a higher tumor ORR than when administered as a 3-h infusion, but does not significantly improve TTP or OS. It has increased hematologic toxicity and decreased neurosensory toxicity [11].

Weekly doses of paclitaxel (80–100 mg/m^2) can be administered continuously for several weeks with minimal myelosuppression. ORR are at least as high as would be expected from every 3-week therapy (53% and 22% in two separate studies) [20, 21], even in patients with anthracycline-refractory MBC. Weekly paclitaxel (80 mg/m^2) was directly compared to every 3-week therapy (175 mg/m^2) in the CALGB 9840 trial [22]. In this trial, weekly therapy was associated with a significantly higher ORR (40% vs. 28%) and longer TTP (9 vs. 5 months), but similar OS and worse neurotoxicity. Thus, the decision paclitaxel weekly versus every 3 weeks should be based upon a balance of toxicity and patient convenience.

ABI-007 (nab-paclitaxel)

ABI-007 (nab-paclitaxel) is Cremophor-free nanoparticle albumin-bound formulation of paclitaxel. Nab-paclitaxel does not require steroid premedication, and can be administered over 30 min without special tubing. Both weekly (100–150 mg/m^2) and every 3 weekly Abraxane are active and well tolerated in taxane-refractory MBC [7, 8]. In one multicenter phase II trial, the objective response rates for patients undergoing first-line and beyond first-line therapy with nab-paclitaxel were 64% and 21%, respectively; and there were no hypersensitivity reactions [8].

Nab-paclitaxel has been compared to paclitaxel in a phase III trial [7] in which 460 patients with MBC were

randomly assigned to nab-paclitaxel (260 mg/m^2 over 30 min without premedication) or standard paclitaxel (175 mg/m^2 over 3 h), both on day 1 every 21 days. Nab-paclitaxel was associated with a significantly higher response rate (33% vs. 19%), and longer TTP (23 vs. 17 weeks). Nab-paclitaxel was associated with no severe hypersensitivity reactions, and less grade 4 neutropenia (9% vs. 22%), but a higher rate of grade 3 sensory neuropathy (10% vs. 2%), which was reversible and short-lived. Nab-paclitaxel is approved in the United States for the treatment of MBC. Despite of all above mentioned advantages over unbound paclitaxel, nab-paclitaxel is significantly more expensive.

Docetaxel

Docetaxel is a semisynthetic analogue of paclitaxel, and like paclitaxel, it is highly effective even in heavily pretreated patients, with ORR up to 60% [5, 6, 23].

Dose and schedule

The standard dose is 100 mg/m^2 over 1 h every 3 weeks. The optimal dose of docetaxel monotherapy was the subject of a randomized trial, in which 527 patients progressing after one prior regimen for metastatic disease, or within 6 months of adjuvant chemotherapy were randomly assigned to 60, 75, or 100 mg/m^2 docetaxel, administered every 21 days [24]. A significant dose-response relationship was observed for tumor ORR (20%, 22%, and 30%, respectively) but not for TTP (13, 15, and 17 weeks, respectively) or OS (10.6, 10.3, and 12.3 months, respectively). The incidence of its toxicities (including grade 3 or 4 neutropenia and febrile neutropenia) was also dose-related.

Docetaxel, like paclitaxel, has been administered in a weekly schedule, at doses of 30–40 mg/m^2 over 1 h, with response rates of 40–50% [25], and as with paclitaxel, is less myelosuppressive [26, 27]. However, weekly therapy is associated with increases in hyperlacrimation, skin- and nail-toxicity, and negatively affects quality of life [28]. Asthenia is particularly common with weekly docetaxel.

Is there a "best" taxane in the setting of MBC?

It is unclear which taxane is superior when taxane monotherapy is considered. In the only Phase III trial that directly compared docetaxel and paclitaxel head-to-head, 449 women who had received prior anthracyclines were randomly assigned to docetaxel (100 mg/m^2) or paclitaxel (175 mg/m^2 over 3 h) every 3 weeks [10]. The docetaxel group had a nonsignificantly higher response rate (32% vs. 25%, $P = 0.1$), modestly but significantly higher median TTP (5.7 vs. 3.6 months, $P = 0.0001$) and improved OS (15.4 vs. 12.7 months, $P = 0.03$). However, both hematologic and nonhematologic toxicity was worse with docetaxel.

Docetaxel has been compared to nab-paclitaxel in a 4-arm randomized Phase II trial recently presented in abstract form by Gradishar et al. [29]. While Phase II trials are not perfect venues to compare agents, docetaxel was outperformed with regard to ORR by nab-paclitaxel in this setting. A Phase III trial should now offer a definitive answer.

Given the results of CALGB 9840, we now know that weekly paclitaxel is superior to every 3 week paclitaxel, casting into doubt the superiority of docetaxel. Similarly, the head-to-head comparison of nab-paclitaxel with standard paclitaxel was a comparison employing every 3 week paclitaxel. At present, it seems reasonable to consider all three agents useful for metastatic breast cancer, but difficult to declare a "best" agent on objective grounds.

Adjuvant and neoadjuvant taxane therapy for early breast cancer

Adjuvant trial designs in the early 1990s were absent of taxanes. By the mid 1990s, the taxanes were included in adjuvant trials; initially in node-positive patients, and subsequently in both node-negative and node-positive patients. The results consistently demonstrated a benefit for taxane-based regimens as a component of adjuvant chemotherapy regimens for early breast cancer. A recent meta-analysis [30] of nine Phase III trials designed to assess if paclitaxel or docetaxel improve survival (included a total of 15,598 patients) found the absolute benefits in DFS and OS in favor of taxane based regimens ranged from 3.3% to 4.6% and from 2.0% to 2.8%, respectively.

Following the initial generation of adjuvant trials (Table 1), and parallel trials conducted in the metastatic setting, investigators then turned to the question of taxane superiority in the adjuvant setting. Is there a "best" taxane, and a "best" dose and schedule?

The *ECOG E1199* trial [31] was conducted to answer this question. A total of 4,950 women with T1-3 N1-2 or T2-3 N0 breast cancer all received AC × 4 followed by randomization to one of four groups for sequential taxane therapy: every 3 weeks paclitaxel (175 mg/m^2), weekly paclitaxel (80 mg/m^2), every 3 weeks docetaxel (100 mg/m^2), or weekly docetaxel (35 mg/m^2). As presented at the 2007 ASCO meeting, while the initial 2 × 2 comparison for drug type and dosage revealed no statistically significant differences, comparison of all four arms revealed

Table 1 Randomized controlled trials included taxanes in the adjuvant therapy for breast cancer

Taxane	Trial	Patients no.	Median follow up (months)	Arms	5-Year DFS (%)	OS (%)
Paclitaxel (P)	MDACC [32]	524	60	8FAC	83 (4 year DFS)	NR
				4P → 4FAC	86	
	CALBG 9344 [33]	3,121	69	4AC	65	77
				4AC → 4P	70	80
	NSABP B-28 [34]	3,060	64.6	4AC	72	85
				4AC → AP	76	85
	HeCOG [35]	595	62	4E → 4CMF	77 (3 year DFS)	90
				4E → 4P → 4CMF	80	93
Docetaxel (D)	US oncology [36]	1,016	66	4AC	80	87
				4DC	86	90
	PACS 01 [37]	1,999	60	6FEC	73.2	86.7
				3FEC → 3D	78.3	90.7
	BCIRG 001 [38]	1,491	55	6FAC	68	81
				6DAC	75	87
	ECOG 2197 [39]	2,889	53	4AC	87 (4 year DFS)	93
				4AD	87	94
	NSABP B-27 [40]	2,404	77.9	AC → surgery	67.7	80.4
				AC → D → surgery	71.1	80.6
				AC → surgery → D	70	78.6
P versus D	ECOG 1199 [31]	4,950	63.8	4AC → P3 × 4	76.9	86.5
				4AC → P1 × 4	81.5	89.7
				4AC → D3 × 4	81.2	87.3
				4AC → D1 × 4	77.6	86.2

DFS, disease-free survival; OS, overall survival; MDACC, M. D. Anderson Cancer Center; F, 5-fluorouracil; A, doxorubicin; C, cyclophosphamide; P, paclitaxel; NR, not reported; CALGB, Cancer and Leukemia Group B; NSABP, National Surgical Adjuvant Breast Project; HeCOG, Hellenic Cooperative Oncology Group; E, epirubicin; P, paclitaxel; D, docetaxel; PACS, Programme Adjuvant Cancer du sein; BCIRG, Breast Cancer Interantinal Research Group; ECOG, Eastern Cooperative Oncology Group; P3, Paclitaxel every 3 weeks; P1, Paclitaxel every week; D3, Docetaxel every 3 weeks; D1, Docetaxel every week

weekly paclitaxel and q3w docetaxel to be superior to q3w paclitaxel with regard to DFS, the primary study endpoint. The incidence of all grade 3–4 toxicity was higher in docetaxel arms, and docetaxel every 3 weeks was the most toxic.

Conclusions

Is the long duel over? The results of E1199, the only large adjuvant trial asking the direct comparison question, suggests that weekly paclitaxel and every 3 week docetaxel represent reasonable adjuvant taxane approaches. This verdict may be a temporary one. We currently lack adjuvant data with nab-paclitaxel, compared either with standard paclitaxel or docetaxel. The evolving therapeutic landscape is also changing, with the addition in recent years of adjuvant HER2-targeted therapy and the advent of genomic technologies and novel adjuvant therapies (e.g., bevacizumab) that may further alter our perception of both risk and benefit. Some stories never end in oncology, but all are altered in the telling.

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