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Adjuvant Taxanes in Breast Cancer: A Critical Re-appraisal

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ABSTRACT

***Purpose*:** *Several studies have reported a positive impact for taxanes in adjuvant breast cancer* (*BC*) *treatment in terms of reduced recurrence and mortality. However the impact of the magnitude on overall survival* (*OS*) *remains partially controversial. Methods*: *We examined the impact of taxane-containing adjuvant therapy for patients with early BC on OS, based on the number of deaths and on the calculated number of patients who need to be treated with taxanes to avoid one death* (*NNT*). *We classified patients in three different groups according to whether taxanes were administered concurrently or sequentially, and whether all treatment arms had the same or different duration.* ***Results*:** 1) *Taxanes in combination therapy*: 8258 *patients* (4373 *with taxanes and* 3885 *without taxanes*), *with* 723 *OS events. Overall survival for taxane-treated patients was* 92.7% *versus* 89.6% *for patients not receiving taxanes. NNT was* 33. 2) *Sequential treatment of unequal duration in the treatment arms*: 14,228 *patients* (7970 *with taxanes and* 6256 *without). Overall survival in taxane-treated patients was* 86% *compared with* 83.2% *for patients not receiving taxanes. NNT was* 44. 3) *Sequential treatment and similar duration in treatment arms*: 9511 *women* (5093 *with taxanes and* 4418 *without*). *Overall survival in patients treated with taxanes was* 87% *versus* 85% *in patients not receiving taxanes. NNT was* 50. *When the results of all these trials were considered together, the NNT stands at* 43 *patients.* ***Conclusion*:** *Taxanes afford a modest increase in overall survival in BC patients regardless of how they are given. Translational trials may well help to improve patient selection in the future.*

***Keywords*:** *Taxanes, Adjuvant Chemotherapy, Early Breast Cancer*

1. Introduction

Several metanalyses [1,2] have reported a positive impact for taxanes in adjuvant breast cancer treatment in terms of reduced recurrence rates and mortality. This reduction was seen regardless of either the kind of taxane used (paclitaxel versus docetaxel), the administration schedule (concurrent versus sequential) in combination with other chemotherapy agents such as the anthracyclines, duration in treatment time (same duration versus differing duration) for chemotherapy regimens in the taxane and control arms, axillary node involvement and hormone receptor status. Some of the published studies [3-12], though not all [13-20], showed an increase in disease-free survival. Furthermore, only in a few of these studies [3,6,7,11] there were higher overall survival, while the impact of the magnitude on overall survival remains partially controversial. This information calls for a re-appraisal of the issue of which patient sub-groups really benefit from the addition of taxanes in adjuvant breast cancer therapy.

2. Methods and Results

We have examined the impact of taxane-containing adjuvant therapy for patients with early breast cancer on overall survival, based on the number of deaths occurring in the different treatment arms and on the calculated number of patients who need to be treated with taxanes to avoid one death (NNT). We classified patients in three different groups of study according to whether the taxanes were administered concurrently or sequentially, and whether all treatment arms had the same or different duration. In all, we reviewed outcomes for 31,997 patients recruited in 18 Phase III clinical trials. There were 7729 DFS events and 4205 OS events.

The first group included patients from clinical trials using taxanes in combination therapy (**Table 1**). In all, there were 8258 patients (4373 with taxanes and 3885 without taxanes) from 6 clinical trials, with 723 OS events. Overall survival for taxane-treated patients was

Table 1. Clinical trials with taxane-combination therapy in the adjuvant treatment of early breast cancer.

Trial (n° patients)	N status	Follow up (months)	Design	HR for DFS (*p* value)	Events for DFS	HR for OS (p value)	N° deaths
Anglo-Celtic, 2005 (363)[13]	+/–	32	AD (183)	NR	45	NR	25
			AC (180)	(0.20)	55	(0.57)	28
BCIRG 001, 2005 (1491)[3]	+	55	TAC (745)	0.72	172	0.7	91
			FAC (746)	(0.001)	227	(0.008)	130
E2197, 2008 (2882)[14]	+/–	79.5	AD (1441)	1.02	257	1.06	116
			AC (1441)	(0.78)	262	(0.62)	123
BIG 02-98, 2008 (1446)[4]	+	62,5	AD→CMF (959)	0.86	252	0.92	6
			AC→ CMF (487)	(0.05)	137	(ns)	4
GEICAM 9805, 2008 (1060)[5]	–	77	TAC (539)	0.68	66	0.76	24
			FAC (521)	(0.014)	95	(0.29)	34
US Oncology, 2009 (1016)[6]	+/–	84	DC (506)	0.74	88	0.69	58
			AC (510)	(0.033)	118	(0.032)	84

A: doxorubicin. C: cyclophosphamide. D: docetaxel. F: fluorouracil. P: paclitaxel. E: epirubicin. M: methotrexate. OS: overall survival. DFS: disease free survival. HR: hazard ratio. NS: not significant. NR: not reported.

92.7% versus 89.6% for patients not receiving taxanes. NNT was 33 patients.

The second group assessed patients recruited on clinical trials using sequential treatment of unequal duration in the different treatment arms (**Table 2**). In all, we studied 14,228 patients (7970 with taxanes and 6256 without) from 9 clinical trials, although we were unable to examine OS survival data in two of these (MD Anderson and ECTO trials). Overall survival in taxane-treated patients was 86% compared with 83.2% for patients not receiving taxanes, with an NNT of 44 patients.

The third group included patients from clinical trials with sequential treatment and similar duration in all treatment arms (**Table 3**). In all, 9511 women from 4 clinical trials (5093 with taxanes and 4418 without) were assessed. Overall survival in patients treated with taxanes was 87% versus 85% in patients not receiving taxanes. NNT was 50 patients in this case.

When the results of all these trials are considered together, the NNT stands at 43 patients.

3. Discussion

This result reflects how only a small number of taxane-treated breast cancer patients actually improve overall survival with adjuvant taxanes. This leads us to wonder which patient population may really benefit from this therapy.

Currently there are no clearly defined prognostic factors for the efficacy of taxanes in adjuvant therapy for early breast cancer with positive or high risk negative axillary lymph nodes. Attempts have been made to link taxane benefits with hormone receptor and Her2 expression in the tumor. In some trials, there was a greater gain from taxanes in patients with hormone-receptor negative tumours [4,7,14,15,16], than in receptor positive cancers.

A retrospective study conducted by CALGB from 3 randomised trials (CALGB 8541, CALGB 9344/INT0148, CALGB 9741), compared the benefit of adjuvant chemotherapy in 6.644 patients with early, lymph-node positive breast cancer between estrogen-receptor positive tumours versus estrogen-receptor negative tumours. The absolute benefit of the optimal chemotherapy regimen (dose-dense chemotherapy in the third study versus suboptimal dose in the first study) was greater in estrogen-receptor negative (ER–) cancers than in estrogen-receptor positive (ER+) cases, with a difference in 5-year DFS of 22.8% for ER– tumours versus 7% for ER+. There were also greater differences in OS for ER– tumours, namely, 16.7% versus 4% for ER+. In all three studies, the gain was greater in ER– than in ER+ tumours from the best chemotherapy regimen [21]. However, this does not mean that hormone receptor positive tumours may or should forgo the benefits of taxanes even though their impact may be more limited in this kind of cancer.

Other research groups have failed to find any difference in hormone receptor expression status and benefit from taxanes [3,6,8,12,17,20]. Moreover, the results of the metanalyses [1,2] found no difference in taxane benefit according to hormone receptor status either, in spite of the fact that most trials studied included similar hormone therapy policies, where tamoxifen was given for 5 years in patients with ER+/PR+ cancer, with only some exceptions. The HeCOG trial [16] included LHRH agonists in their hormone therapy for 1 year together with tamoxifen for pre-menopausal women with positive hormone receptors. The ECTO trial [9] treated all their patients with tamoxifen up to June 2000; after that time, tamoxifen was given only to women with positive hormone receptor status. In the NSABP B-28 trial [8] all women over 50 years of age received tamoxifen regardless of receptor status, while women aged <50 years only received tamoxifen if hormone receptor positive. In this study, tamoxifen was also given concurrently with chemotherapy which may lessen the efficacy of chemotherapy. In the PACS 01 trial [11], initially only post-meno-

Table 2. Clinical trials in the adjuvant treatment of early breast cancer using taxanes sequentially and with unequal duration.

Trial (nº patients)	N status	Follow up (months)	Design	HR for DFS (*p* value)	Events for DFS	HR for OS (p value)	N° deaths
MD Anderson, 2002 (524)[15]	+/–	60	P→FAC (265) FAC (259)	0.7 (0.09)	39 53	NR	23 24
CALGB 9344, 2003 (3121)[7]	+	69	AC→P (1551) AC (1570)	0.83 (0.002)	491 563	0.82 (0.006)	342 400
He COG, 2005 (595)[16]	+/–	62	E→P→CMF (297) E→CMF (298)	0.93 (0.55)	91 98	NR (0.38)	53 61
NSABP-B28, 2005 (3060)[8]	+	64	AC→P (1529) AC (1531)	0.83 (0.006)	400 463	0.93 (0.46)	243 255
NSABP B27, 2006 (2404)[17]	+/–	77.9	AC→S→D (799) AC→D→S (803) AC→S (802)	0.9 (0.24)	254 260 276	1.08 (0.51)	171 156 157
TAXIT 216, 2006 (972)[18]	+	53.6	E→D→CMF (486) E→CMF (486)	0.79 (0.057)	115 138	0.72 (0.08)	51 70
BIG 02-98, 2008 (1441)[4]	+	62.8	A→D→CMF (960) A→CMF (481)	0.86 (0.05)	214 129	0.92 (ns)	3 7
ECTO, 2009 (1355)[9]	+/–	76	AT→CMF→S (451 S→AT→CMF (451) S→A→CMF (453)	0.73 (0.03)	NR	0.8 (0.21)	NR
HORG, 2010 (756)[10]	+	62.5	D→ EC (378) FEC (378)	NR (0.04)	108 125	NR 0.53	74 75

A: doxorubicin. C: cyclophosphamide. D: docetaxel. F: fluorouracil. P: paclitaxel. E: epirubicin. M: methotrexate. S: surgery. OS: overall survival. DFS: disease free survival. HR: hazard ratio. NS: not significant. NR: not reported.

Table 3. Clinical trials in the adjuvant treatment of early breast cancer using taxanes sequentially with similar treatment duration.

Trial (nº patients)	N status	Follow up (months)	Design	HR for DFS (*p* value)	Events for DFS	HR for OS (p value)	N° deaths
PACS 01, 2006 (1999)[11]	+	60	FEC→D (1003) FEC (996)	0.80 (0.012)	218 264	0.73 (0.017)	100 135
MA21, 2010 (2104)[19]	+/–	30.4	AC→ P (702)(i) ddEC→ P(701)(ii) CEF (701) (iii)	i vs. ii 1.49 (0.005) ii vs. iii 0.89 (0.46)	112 70 79	NR	65 47 50
GEICAM 9906, 2008 (1246)[12]	+	66	FEC→P (614) FEC (632)	0.77 (0.02)	146 193	0.78 (0.11)	73 95
TACT, 2008 (4162)[20]	+/–	62	FEC→D (2073) FEC/E→CMF (2089)	0.95 (0.44)	517 539	0.99 (0.91)	374 378

A: doxorubicin. C: cyclophosphamide. D: docetaxel. dd: dose dense. F: fluorouracil. P: paclitaxel. E: epirubicin. M: methotrexate. OS: overall survival. DFS: disease free survival. HR: hazard ratio. NR: not reported.

pausal women were treated with tamoxifen regardless of receptor status, but this was later extended to pre-menopausal women with positive hormone receptor status. So hormone receptor status is insufficient alone and is not the only predictive factor for taxane efficacy.

Hayes *et al.* [22] reported in their study on 1500 patients from the CALGB 9344 trial how the addition of paclitaxel to adjuvant therapy with doxorubicin plus cyclophosphamide was associated with significantly lower relapse and mortality rates in Her2 positive patients, regardless of ER expression status. An interesting finding here is that the group of patients with Her2 negative, ER positive breast cancer, *i.e.* over half the patients with breast cancer included in the trial, did not gain any benefit from the addition of paclitaxel. However, these outcomes do belong to an unplanned retrospective analysis of patient subgroups and while the result of such a study is useful to generate hypotheses, we cannot draw definitive conclusions. Therefore, these results should be confirmed prospectively before they become a turning point for a change in clinical practice.

We may conclude that taxanes afford a modest increase in overall survival in breast cancer patients regardless of how they are given. This may well be due to the fact that the gain is not seen homogeneously across all patients, and becomes even weaker among women where this therapy is of no advantage given the heterogeneity of breast cancer as a disease. Unfortunately, we have no factors capable of predicting the benefit of taxanes that could be applied in clinical practice so as to

optimize their use. Hormone receptor expression and Her2 status alone have scant predictive value for the efficacy of taxanes. Translational trials, like the Trans TACT trial, are of the utmost interest and the knowledge generated may well help to improve patient selection in the future [20].

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