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ORIGINAL ARTICLE

Taxanes in the adjuvant treatment of node-negative breast cancer patients

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Summary

Purpose: *Although the use of regimens with adjuvant taxanes is a standard approach in node-positive breast cancer, the use of taxanes in node-negative breast cancer is still controversial. In this search, we aimed to evaluate the data about the use of taxanes in high-risk node-negative patients.*

Methods: *Studies were retrieved by searching the Pubmed database. Randomized phase III studies on the use of regimens with adjuvant taxanes in early-stage breast cancer were screened and, among them, the studies that included node-negative patients were included in the evaluation.*

Results: *Data on the adjuvant use of taxanes in node-negative patients were classified into 3 categories: a) studies that evaluated both node-positive and node-negative patients; b) meta-analyses on the use of adjuvant taxanes; and c) studies that included node-negative patients alone. The results of the studies that evaluated both node-positive and node-negative patients and the meta-analyses were evaluated according to the node-negative subgroup analyses. While two of these studies did not show difference in disease-free survival (DFS) for the node-negative subgroup, one study showed a difference in DFS. The only data for the adjuvant use of taxanes in only node-negative breast cancers belong to GEICAM 9805 study and, according to its results, docetaxel provided a difference in DFS in high-risk node-negative patients.*

Conclusion: *Data about the adjuvant use of taxanes in node-negative patients are limited compared to the studies in which both node-positive and node-negative subgroups are evaluated. In the light of these studies, it is impossible to make a comment about the use of taxanes in node-negative patients. However, GEICAM 9805 study has shown positive results on DFS in high-risk node-negative breast cancer patients with adjuvant taxanes.*

Key words: adjuvant, breast cancer, disease-free survival, lymph node negative, taxanes

Introduction

Lymph node-negative breast cancers account for approximately 50-60% of all breast cancers. Of these patients, 30-40% are high-risk node-negative patients [1]. According to St Gallen consensus, high-risk node-negative breast carcinoma is characterized by pT >2 cm, grade 2-3, HER-2/neu gene amplification or overexpression, negativity of estrogen and progesterone receptors or age < 35. A patient who has a tumor with any of these characteristics is considered to be a high-risk patient [2].

In early-stage breast cancer, cyclophosphamide-methotrexate-5 fluorouracil (CMF) has been the first combination regimen, and, in the following years, the demonstration of the anthracyclines' efficacy led to the predomination of anthracycline-based regimens [3-5]. The efficacy of taxanes has been first shown in metastatic breast cancer, and thereafter, in the adjuvant therapy of node-positive breast cancer as concomitant with anthracycline or consecutive to anthracycline therapeutic schedules [6-10]. Today, as one step forward, the efficacy of taxanes is being evaluated in patients with high-risk node-negative disease. Based on the literature, the data about the adjuvant use of taxanes in such patients may be categorized into 3 groups:

1. Phase III studies that evaluated node-positive and high-risk node-negative patients.
2. Meta-analyses for taxanes in the adjuvant therapy of breast cancer.

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3. Studies that included only patients with high-risk node-negative breast cancer.

The purpose of this study was to summarize the data about the adjuvant use of taxanes in high-risk node-negative breast cancer patients.

Methods

To investigate this topic, the relevant English language studies were identified through Medline. For our search we used the key words breast cancer, taxanes docetaxel, paclitaxel, adjuvant chemotherapy and lymph node. The references from the identified articles were also reviewed for additional sources. Studies that included lymph node-negative patients and comparing the addition of taxanes to a standard chemotherapy arm were included in our study.

Results

Phase III studies that evaluated node-positive and high-risk node-negative patients

The first study that included node-positive patients as well as high-risk node-negative patients was conducted by Buzdar et al. (MDACC2002) [11]. A total of 524 patients (33% non-operated, neoadjuvant-intended) were randomized to receive either 4 cycles of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) or 4 cycles of paclitaxel. Thereafter, both arms continued the therapy with 4 cycles of FAC. Of the patients, 28% were node-negative. During the 5-year follow-up, both patient groups showed a trend for significance regarding DFS (83 vs. 86%, HR=0.70, 95% CI: 0.47-1.07, p=0.09). However, no subgroup analysis was performed for node-negative patients [11]. Again, in a phase III study conducted by Hellenic Cooperative Oncology Group in high-risk breast cancers, a total of 595 patients were randomized to 3 cycles of epirubicin-3 cycles of paclitaxel-3 cycles of CMF or to 4 cycles of epirubicin-4 cycles of CMF. In this study, only 2% of the patients were node-negative. In both patient groups, no difference in DFS (68 vs. 70%, p=0.55) and OS (81 vs. 84%, p=0.38) was observed, probably due to the small number of node-negative patients. DFS and OS were not evaluated in this patient group [12].

In another study (North American Breast Cancer Intergroup Trial E 2197 study), approximately 2,000 node-positive and high-risk node-negative patients were randomized to doxorubicin, cyclophosphamide (AC) and to doxorubicin, docetaxel (AT) arms. Of the patients, 66% were node-negative. During the 5-year follow-up, none of the patient groups showed a significant difference of DFS (in both arms, 85%, HR=1.02, 95% CI: 0.86-1.22, p=0.78) or OS (91 vs. 92%, HR=1.06, 95% CI: 0.85-1.31, p=0.62). Again, in the subgroup analysis, node-negative patients did not show a statistically significant difference (HR: 1.06, 95% CI: 0.84-1.32, p: not reported) [13]. In another study that enrolled high-risk node-negative patients (UK TACT study), 4,162 patients were randomized to receive 8 cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) or 4 cycles of epirubicin and 4 cycles of CMF vs. 4 cycles of FEC and 4 cycles of docetaxel. Of the patients, 20% were node-negative. During the 5-year follow-up, none of the patient groups showed a significant difference of DFS (74.3 vs. 75.6%, HR=0.95, 95% CI: 0.85-1.08; p=0.44) or OS (HR=0.99, 95% CI: 0.86-1.14, p=0.91). Again, in the subgroup analysis, node-negative patients did not show a statistically significant difference of DFS (HR=0.88, 95% CI: 0.88-1.25) [14]. In the USON 9735 study, which is one of the larger studies conducted for early-stage breast cancer, 1,016 patients were randomized to receive 4 cycles of AC and 4 cycles of AT. The main aim of this study was to investigate the efficacy of an anthracycline-free regimen in the treatment of early-stage breast cancer, rather than to determine whether the addition of taxanes to the therapy provides an additional benefit. Approximately half of randomized patients were high-risk node-negative patients. To date, 5-year, and thereafter 7-year results of the study were reported. For all patient groups, during 5-year follow-up, the difference of DFS was significant (80 vs. 86%, HR=0.67; 95% CI: 0.50-0.94, p=0.015), while the difference of OS did not reach significant level (87 vs. 90%, HR=0.76; 95% CI: 0.52-1.1; p=0.13). During 7-year follow-up, both DFS (75 vs. 81%, HR=0.74; 95% CI: 0.56-0.98, p=0.033), and OS (82 vs. 87%, HR=0.69; 95% CI: 0.50-0.97, p=0.032) were found to be significantly better in the docetaxel arm. For node-negative patients, the subgroup analysis did not show a significant difference between the arms in 5-year follow-up (HR: 0.73, 95% CI: 0.42-1.27, p: not reported), however, no subgroup analysis results were given for node-negative patients in the 7-year follow-up [15,16].

In another study called European Cooperative Trial in Operable Breast Cancer (ECTO), 1,355 patients were randomized to 3 treatment arms. The first arm was given 4 cycles of doxorubicin and 4 cycles of CMF; the second arm was given 4 cycles of doxorubicin-paclitaxel and 4 cycles of CMF; and the third arm was given 4 cycles of doxorubicin-paclitaxel and 4 cycles of CMF before operation. Of all patients, one third was in a neoadjuvant group and approximately 40% were in a high-risk node-negative group. When the results were compared in terms of treatment arms, in 7-year follow-up, the addition of paclitaxel provided

significant difference in DFS (69 vs. 76%, HR=0.73, 95% CI: 0.57-0.97, p=0.033), while OS was not different between the groups (82 vs. 85%, HR=0.70, 95% CI: 0.51-0.96, p=0.21). For node-negative patients in the postoperative therapeutic arms, it was observed that the addition of paclitaxel provided an improvement in DFS (HR=0.07) [17].

When the results of these studies [11-17] are evaluated, it is impossible to clearly comment about the use of taxanes in node-negative patients (Table 1).

Meta-analyses for taxanes in the adjuvant therapy of breast cancer

The use of taxanes in the adjuvant therapy of breast cancer was evaluated in a meta-analysis conducted by Bria et al., which included a total of 9 randomized phase III studies, 5 conducted with paclitaxel and 4 with docetaxel, and in a total of 15,500 patients. This meta-analysis demonstrated that, in all patient groups, the addition of taxanes led to a significant improvement in both DFS (HR=0.86, 95% CI: 0.81-0.90, p<0.0001) and OS (HR=0.87, 95% CI: 0.81-0.93, p<0.0001). It was observed that, in the subgroup analysis, the significant differences of DFS and OS were still present in node-positive patients, in those who received taxanes subsequently or concomitantly and in those who used both docetaxel and paclitaxel. However, a subgroup analysis was not reported for node-negative patients [18].

In another meta-analysis performed by Bria et al., 7 randomized studies evaluated the efficacy of the addition of taxanes in the neoadjuvant therapy for breast cancer. However, as these studies were completely consisted of neoadjuvant arms, it was not possible to make a comment about the use of taxanes as an adjuvant therapy in high-risk node-negative patients [19].

The largest meta-analysis over the use of taxanes as adjuvant therapy in breast cancer was performed by de Laurentis et al. [20]. This meta-analysis included a total of 13 studies and 22,903 patients. Adjuvant and neoadjuvant studies were analysed together. When all patients were evaluated, it was seen that the addition of taxanes significantly improved both DFS (HR=0.83, 95% CI: 0.79-0.88, p<0.00001) and OS (HR=0.83, 95% CI: 0.76-0.91, p=0.0001). Although results of subgroup analyses were given for different parameters, such as age, menopausal status, receptor status, N1-3 vs. N4+, no subgroup analysis was performed for node-negative patients [20].

Although the results of this meta-analysis strongly supported the use of taxanes in node-positive patients, it was not possible to make a comment about the use of taxanes in node-negative breast cancer.

Studies that included only patients with high-risk node-negative breast cancer

GEICAM 9805 has been the only study in which the efficacy of taxanes was evaluated only in node-negative patients. A total of 1,066 high-risk node-negative patients were randomized to receive either 6 cycles of FAC or 6 cycles of docetaxel, doxorubicin, cyclophosphamide (TAC). When evaluated for survival, 77-month follow-up showed a significantly better DFS in the TAC arm (81.8 vs. 87.8, HR=0.68; 95% CI: 0.49-0.93; p=0.01), but no significant difference was observed for OS between the two arms (93.5 vs. 95.2%, HR=0.76; 95% CI: 0.45-1.26; p=0.29). In the subgroup analysis for age, menopausal status, hormone receptor status, tumor diameter and grade 2-3, it was observed that the patients had statistically significant benefits from TAC. In the subgroup analysis, no difference was found between the groups for HER-2 positive or grade I patients [21]. However, the small number of HER-2 positive patients should be considered.

According to the results of GEICAM 9805, docetaxel proved to efficiently increase DFS in node-negative patients.

Discussion

Studies that investigated the role of taxanes in early-stage breast cancer were generally conducted in node-positive patients. However, after the efficacy of taxanes in node-positive patients has been proven, an answer has been searched for the following question: "Are taxanes efficient in high-risk node-negative patients as well?" To date, 6 randomized phase III studies and 2 meta-analyses evaluated the efficacy of taxanes in both node-positive and node-negative patients. In 3 of these randomized studies, subgroup analyses did not show a difference in survival in high-risk node-negative patients [13-15]. In the USON 9735 study, 5-year results did not reveal a difference of DFS in node-negative patients, while 7-year results did not include a subgroup analysis for node-negative patients [15,16]. Again, as no subgroup analysis was included for node-negative patients in the study performed by Buzdar et al., and due to the small number of node-negative patients in the study performed by Hellenic Cooperative Oncology Group, it is not possible to make a comment about the efficacy of taxanes in high-risk node-negative patients based on these two studies [11,12]. Among the available randomized studies, only the ECTO study showed that node-negative patients benefited as much as node-positive patients with the use of taxanes. However, here, since HR was given,

Table 1. Selected randomized phase III trials in node negative breast cancer

Trial [Ref. no.]	*Patients N*	*Percent of node negative patients*	*Median FU (months)*	*All patients DFS*		*All patients OS*		*Node negative DFS*		*Node negative OS*	
				HR (95% CI)	*p-value*	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*	*HR (95% CI)*	*p-value*
MDACC2002 [11]			60		0.09	NR	NR	NR	NR	NR	NR
4FAC+4FAC	259	24		1							
4P+4FAC	265	32		0.7 (0.47-.07)							
Hellenic [12] [WRONG]				NR	0.55	NR	0.38	NR	NR	NR	NR
3E+3P+3CMF	297	2	62	68% *		81%					
4E+4CMF	298	2		70%		84%					
E2197 [13]			80		0.78		0.62		NR	NR	NR
4AC	1441	65		1		1		1			
4AD	1441	66		1.02 (0.86-1.22)		1.06 (0.85-1.31)		1.06 (0.84-1.32)			
TACT [14]			62		0.44		0.91	NR	NR	NR	NR
8FEC or 4E+4CMF	2089	19.9		1		1					
4FEC + 4D	2073	20.2		0.95 (0.85-1.08)		0.99 (0.86-1.44)					
USON [15]			60		0.015		0.13		NR	NR	
4 AC	510	49		1		1		1			NR
4 DC	506	47		0.67 (0.50-0.94)		0.76 (0.52-1.1)		0.73 (0.42-1.27)			
USON [16]			84		0.033				NR	NR	
4 AC	510	49		1		1	0.32	NR			NR
4 DC	506	47		0.74 (0.56-.98)		0.69 (0.50-0.97)					
ECTO [17]			76		0.03				NR	NR	
4A+4CMF	453	40		1		1	0.21	1			NR
4AD+4CMF	451	38		0.73		0.80		0.71			
GEICAM 9805 [21]			77		0.01		0.29		0.01		0.29
6FAC	521	100		1		1		1		1	
6TAC	539	100		0.68 (0.49-0.93)		0.76 (0.45-1.26)		0.68 (0.49-0.93)		0.76 (0.45-1.26)	

*5-year DFS, F: 5-fluorouracil, A: doxorubicin, C: cyclophosphamide, D: docetaxel, P: paclitaxel, E: epirubicin, M: methotrexate, NR: Not reported, FU: follow up, DFS: disease free survival, OS: overall survival, CI: confidence interval, HR: hazard ratio

but 95% CI interval, median DFS and OS survival or p-value were not given, it is not possible to make a comment about the significance of the outcome [17].

When meta-analyses over the efficacy of taxanes in early-stage breast cancer were considered, and since only one of 3 meta-analyses contained neoadjuvant studies, it was not suitable to make a comment about the use of taxanes in the adjuvant setting [19]. However, two large meta-analyses comprehensively evaluated the efficacy of taxanes in early-stage breast cancer. In the meta-analyses of both Bria et al. and de Laurentis et al., it was observed that the use of taxanes provided significant improvement in both DFS and OS. In both analyses, only results for node-positive patients were given in the subgroup analysis [18,20]. Based on the available results of meta-analyses, it is not possible to make a comment about the efficacy of taxanes in node-negative breast cancer.

The GEICAM 9805 study has been the first and only study performed to draw conclusions over the use of taxanes in node-negative patients. The addition of taxanes provided an absolute decrease of 8% in the recurrence rate of node-negative patients. When the groups were evaluated for recurrence, it was seen that TAC particularly decreased locoregional recurrence (4.1% in FAC arm, 0.7% in TAC arm), but did not provide an important advantage in the prevention of distant metastasis (7.3% in FAC arm, 6.3% in TAC arm) [21]. In both groups, more than half of the patients had undergone breast-conserving surgery at the time of diagnosis. It was observed that the main difference between TAC and FAC occurred in patients who had undergone breast-conserving surgery. In patients who had undergone breast-conserving surgery, locoregional recurrence was observed in 4 patients in the TAC arm and in 14 in the FAC arm. Nevertheless, from patients who had undergone mastectomy, 7 patients in each arm showed locoregional recurrence. Based on these results, the study should also be evaluated for the adequacy of the local therapeutic modalities. However, despite all these concerns, the GEICAM 9805 study is unique for being the first and only study that investigated the efficacy of taxanes in high-risk node-negative patients. The NCT01222052 and NCT00129389 studies, which are still ongoing, will further elucidate the role of taxanes in node-negative breast cancer [22,23].

Conclusion

The role of taxanes in node-negative patients is controversial, but based on the results obtained from the first and only study conducted to date, GEICAM 9805, which will be considered as valid until the time of publication of newer data about this subject, the adjuvant use of taxanes provides a difference of DFS in high-risk node-negative patients.

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