

Evaluation of Docetaxel vs. Tamoxifen in Combined Therapies Based on Overall Survival Rate (OSR) Endpoint among Female Breast Cancer Patients

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Abstract

In this review, overall survival rate (OSR) result and safety data were evaluated based on data from four clinical trials on combined therapies of Docetaxel and Tamoxifen among breast cancer patients, which were published in peer-reviewed journals. Data was extracted from single treatment trials of Docetaxel plus Cisplatin, and Tamoxifen plus Vorinostat, and randomized trials of Docetaxel plus Capecitabine, and Tamoxifen plus Buserelin. Docetaxel was found to have slightly longer OSR than Tamoxifen in combined therapies, and it has better individual strength in combined therapies based on OSR comparison in the trials' treatment arms. However, a considerable number of toxicities caused by combined therapies of both drugs negates the superiority of the efficacy of combined therapies of one of the drugs over the other. Although other combined cancer drugs boost efficacy of Docetaxel and Tamoxifen in the combined therapies, they should be selected to minimize the toxicities in combined therapies of both drugs.

Keywords: Docetaxel; Tamoxifen; Overall survival rate; OSR; Breast cancer

Introduction

Breast cancer drugs are one of the most common cancer drugs produced among cancer drugs. According to Buffery [1], 16.59% of 440 cancer drugs produced as of March 12, 2015 were breast cancer drugs. In spite of several cancer drugs that have been produced by pharmaceutical companies, the search for effective treatment therapies for breast cancer continues. In addition, the high occurrence of breast cancer among women justifies the search for effective therapy for the disease. According to the International Agency for Research on Cancer (IARC), breast cancer is the most commonly occurring cancer after lung cancer in the world [2]. In the United States, 1 in 8 women are predicted to have metastatic breast cancer during their lifetime [3]. The search for effective breast cancer therapy that can achieve improved survival and complete remission of breast cancer patients has increased popularity of combined therapies of two or more cancer drugs by cancer researchers.

Review Rationale

Docetaxel and Tamoxifen are anti-cancer drugs that have shown impressive treatment among the female breast cancer patients population. Docetaxel, which trade name is Taxotere, is a chemotherapy drug that has been used for different stages of breast cancers - early, advanced stage, and metastatic breast cancers. The drug, which works by blocking cell division and spread of cancer cells, has the capability for increased tolerability and efficacy among breast cancer patients, including metastatic breast cancers. According to Esteva [4], the improved survival rate among breast cancer patients that have resistance to anthracycline, has increased popularity of Docetaxel as one of the most effective drugs against breast cancer. On the other hand, Tamoxifen is a hormone-based cancer drug, which functions by blocking the estrogen hormone from reaching cancer cells

through the positive hormone receptors on cancer cells. The drug has been used for breast cancer for different purposes such as slowing down the cancer recurrence and disease progression.

Combined therapies of either Docetaxel or Tamoxifen with other cancer drugs have been yielding good results in clinical trial phases; either as single treatment, prospective randomized, or randomized clinical trials. Surrogate cancer endpoints include Progression-free survival (PFS), Overall survival rate (OSR), Complete response, Objective response rate (ORR), and Disease-free survival (DFS), Clinical benefit rate, among others [5]. Among all these endpoints, OSR is regarded as the most practical endpoint to measure the effectiveness of the oncology treatment including combined cancer therapies. The endpoint is usually measured as either calculating the timeframe at which half of the clinical trial patient population are still alive (Median OS), or by calculating percentage of number of patients that are still alive in different time intervals (1, 2 or 5 years) in a clinical trial [6].

There are some similarities and differences between the combined therapies of Docetaxel and Tamoxifen, which should provide objective evaluation in this review. The similarities and differences will be limited to factors such as efficacy, safety issues, and individual strength based on median OSR evaluation data analysis. This paper will focus on the research perspective that, while Docetaxel and Tamoxifen have been leading anti-cancer drugs among female breast cancer patients, the difference in treatment result based on OSR endpoint when combined with other cancer drugs makes one of the drugs more promising than the other. Although combined therapies of either Docetaxel or Tamoxifen may be superior in overall survival than the other, some factors such as breast cancer type and safety issues may make neither of the combined therapies of the drugs more effective than the other.

Method and Data Extraction

Four peer-reviewed articles on clinical trials were selected from the PubMed and AT Still One Search databases, for the evaluation of combined therapies of Docetaxel (DOC) and Tamoxifen (TAM). Data that were extracted include the clinical trial phase, number of treatment arms, population number, median age, median OSR, and adverse events. Among the clinical trials, two are single treatment arm clinical trials – Phase II trial of combined therapy of DOC and CIS

(DOC+CIS), and Phase II of TAM and VOR (TAM+VOR) (Tables 1 and 2). The other two are double-blinded randomized trials: Phase III trial, which has two treatment arms of DOC, and DOC + CAP, and randomized trial, which has three treatment arms of TAM, Buserelin (BUS), and TAM + BUS. The age range of the breast cancer population (n=754) in the four clinical trials is between 25 and 79 years old, and mean age is 50.5 years old (Tables 1 and 2).

	Intervention (Clinical Trial)	Number of Treatment Arms	Treatment Arms			Pop (n)	Median Age	Median Overall Survival Rate (months)		
1	Phase II	1	N/A	DOC+CIS	39	51	N/A	23		
2	Phase III Randomized	2	DOC (n=256)	DOC+CAP (n=255)	511	52	11.5	14.5		

Note: Phase II trial of Docetaxel (DOC) and Cisplatin (CIS) is from Se Hoon et al. [7]; and Phase III Randomized trial of Docetaxel (DOC) and Capecitabine (CAP) is from O'Shaughnessy et al. [9]

Table 1: Phase II trial of Docetaxel (DOC) and Cisplatin (CIS), and Phase III Randomized trial of Docetaxel (DOC) and Capecitabine (CAP).

	Intervention (Clinical Trial)	Number of Treatment Arms	Treatment Arms			Pop (n)	Median Age	Median Overall Survival Rate (months)		
1	Phase II	1	N/A	N/A	TAM+VOR	43	56	N/A	N/A	29
2	Randomized Trial	3	TAM (n=54)	BUS (n=54)	TAM+BUS (n=53)	161	43	35	30	44

Note: Phase II trial of Tamoxifen (TAM) and Vorinostat (VOR) is from Munster et al. [8]; and Phase III Randomized trial of Tamoxifen (TAM) and Buserelin (BUS) is from Klijen et al. [10]

Table 2: Combined therapies of Phase II trial of Tamoxifen (TAM) and Vorinostat (VOR), and Phase III randomized trial of Tamoxifen (TAM) and Buserelin (BUS).

Results

Similarities between combined therapies of Docetaxel and Tamoxifen

Combined therapies of Docetaxel (DOC) and Tamoxifen (TAM) share few similarities based on factors such as improved survival rate, good drug interaction with combined cancer drugs, and presence of safety issues. Based on the median OSR data in Tables 1 and 2, combined therapies of both DOC and TAM showed effective results through improved overall survival among patients in single treatment arms. In the Phase II trial of single treatment of DOC and CIS, the combined therapy was found to be effective and safe for the anthracycline-resistant metastatic breast cancer patients [7]. For the Phase II trial of a single treatment group of TAM and Vorinostat (VOS), the median OSR was improved to up to 29 months with effective tolerability and effectiveness among hormone resistant cancer patients [8]. In addition, both drugs, DOC and TAM produced promising results in a Phase III randomized trial of two treatments,

and a randomized trial of three treatment arms respectively. The DOC and CAP treatment arm was 3 months longer in median OSR than the treatment arm with DOC alone among patients that have been previously treated with anthracycline [9]. While median OSR was 5 months longer in TAM treatment than the BUS treatment group, median OSR in combined therapies of TAM and Buserelin (BUS) treatment group were 9 and 14 months longer than TAM and BUS treatment groups respectively (Table 2) [10].

Although combined therapies of Docetaxel and Tamoxifen in the four selected clinical trial evaluations showed improved median OSR among the patients, each of the four combined therapies in Tables 1 and 2 presented some safety issues. Among serious adverse events presented, some were Grade 3 and 4, which define some level of toxicities in combined therapies of DOC and TAM among breast cancer patients in the studies. The leading toxicities among the four combined therapies of both DOC and TAM are neutropenia and hot flashes (Table 3).

	DOC Combined Therapies			TAM Combined Therapies		
	Clinical Trials	All Adverse Events (AEs)	Grade 3 & 4 AEs	Clinical Trials	All Adverse Events (AEs)	Grade 3 & 4 AEs
1	DOC+CIS	Febrile Neutropenia	Febrile Neutropenia	TAM+BUS	Vaginal Bleeding	

		Neutropenia	Neutropenia		Hot flashes	
		Thrombocytopenia	Thrombocytopenia			
		Nausea/vomiting	Nausea/vomiting			
		Oral mucositis	Oral mucositis			
		Asthenia	Asthenia			
		Peripheral neuropathy	Peripheral neuropathy			
		Hearing impairment				
		Renal insufficiency				
2	DOC+CAP	Neutropenic fever	Neutropenic fever	TAM+VOR	Fatigue	Fatigue
		Neutropenia	Neutropenia		Nausea	Neutropenia
		Stomatitis	Stomatitis		Vomiting	Lymphopenia
		Diarrhea	Diarrhea		Diarrhea	
		Nausea	Nausea		DVT/PE	
		Hand-foot syndrome	Hand-foot syndrome		Anorexia/weight loss	
		Alopecia	Alopecia		Mucositis	
		Fatigue/asthenia	Fatigue/asthenia		Hepatic dysfunction (ALT/ST)	
					Hyperglycemia	
					Alopecia	
					Thrombocytopenia	
					Leukopenia	
					Neutropenia	
					Lymphopenia	
					Anemia	
<p>Note: Phase II Trial of Tamoxifen (TAM) and Vorinostat (VOS) is from Munster et al. [8]; and Phase III Randomized trial of Tamoxifen (TAM) and Buserelin (BUS) is from Klijn et al. [10]</p>						

Table 3: Safety issues in the selected clinical trials of Docetaxel (DOC) and Tamoxifen (TAM) combined therapies.

Difference between combined therapies of Docetaxel and Tamoxifen

Based on Table 1, the difference between combined therapies of DOC with Cisplatin (CIS), in the single treatment arm of Phase II trial and Capecitabine (CAP) in randomized Phase III trials confirmed improved efficacy of DOC in combined therapies. The difference between the median OSR in DOC + CIS and DOC + CAP was 8.5 months (Table 1). Comparing this to the difference in combined therapies between TAM + VOR and TAM + BUS, which is 15 months (Table 2), indicates DOC has better tolerability in its combined therapies than TAM in combined therapies. Based on the evaluation of extracted data in Tables 1 and 2, the individual strength of both DOC and TAM can be analyzed based on the median OSR between their combined therapies in the treatment arms containing each of them alone.

In the data extracted from analysis on the randomized Phase III trial of DOC with and without CAP, there was no significant difference between median OSR in the treatment arm of DOC without CAP, and DOC with CAP treatment. Median OSR in DOC group was 11.5 months, compared to 14.5 median OSR in the DOC and CAP treatment group [9]. The difference was higher in the comparison in the randomized trial of TAM and BUS. Difference between median OSR of TAM and BUS, and TAM treatment groups was 9 months in equal number of breast cancer patients of 53 and 54 respectively [10]. Docetaxel seems to possess stronger individual strength than Tamoxifen in combined therapies with other breast cancer drugs. Docetaxel was found to be the only single chemotherapy cancer drug with more tolerability among pre-treated alkylating breast cancer patients, and showed a promising outcome in terms of efficacy over anthracycline doxorubicin in clinical trial [4].

Based on safety data in Table 3, the DOC combined therapies had consistent adverse events (AEs) in the two selected clinical trials of

combined therapies of DOC with CAP and CIS respectively. There were 16 AEs in both clinical trials with the leading safety toxicity being neutropenia. According to Se Hoon et al. [7], 39% of patients in the Phase II trial of combined therapy of DOC and CIS had severe hematological toxicity of neutropenia.

Although hot flashes are a known side effect with combined therapies of TAM, in their evaluation on TAM combined therapies, Smith et al. [11] found hot flashes and thromboembolism occurred more in the TAM treatment group, and the combined Anastrozole and TAM group. However, based on Table 3, there is no consistency between the AEs that occurred in the two selected clinical trials on combined therapies of TAM with VOR and BUS respectively. Overall, while DOC combined therapies have better median OSR compared to when DOC is used alone, DOC combined therapies presented more Grade 3 and 4 AEs than combined therapies of TAM that were evaluated (Table 3).

Discussion

While several clinical trials have been carried out for the evaluation of combined therapies of DOC and TAM, the combined therapies of DOC and TAM shared some similarities based on results that both have improved survival for female breast cancer patients. Although combined therapies of both drugs are effective, they presented safety issues among clinical trial patients. The differences are based on their individual strength in their respective combined therapies, number and types of safety issues presented, and the OSR comparison between the two drugs and their combined cancer drugs.

Docetaxel (DOC) combined therapies were found to be associated with hematological issues, compared to general safety issues including hot flashes, vaginal bleeding, and neutropenia, which were present in Tamoxifen (TAM) combined therapies (Table 3). The consistency in the safety issues presented in Table 3 on combined therapies of DOC makes them easy to manage. Neutropenia was found to be the leading toxicity with combined therapies of Docetaxel. Similar safety analysis such as one presented by Lee and Nan [12] confirmed that severe hematological toxicity such as neutropenia was common with Docetaxel combined regimens among breast cancer patients.

Overall, Docetaxel combined therapies were found to be slightly more effective in improved overall survival based on the median OSR comparison between the two selected trials for Docetaxel combined therapies, and Tamoxifen combined therapies. There was a slight difference of median OSR in DOC plus CIS and DOC plus CAP, compared with the higher difference of median OSR between TAM plus BUS and TAM and VOR. This result suggests Docetaxel has more efficacy and tolerability than Tamoxifen when used in combined therapies among clinical trial cancer patients. In addition, the combined drugs used in the combined therapies of Docetaxel and Tamoxifen contribute to the overall survival result and clinical outcome. The combined cancer drug used with either Docetaxel or Tamoxifen serve some clinical purposes, which include resistance management among patients, and enhancement of efficacy. Lee et al. [13] found out that Capecitabine was more effective with Docetaxel in combined therapies (17% Pathological complete response (pCR)) among Hormone Receptor (HR)-positive breast cancer than combined therapy of doxorubicin and cyclophosphamide (3% pCR). In the combined therapy of TAM with VOR, VOR worked with TAM to manage hormone resistance among estrogen response (ER)-positive metastatic breast cancer [8].

Although the other combined drugs used in Docetaxel therapies served effective clinical purpose, individual strength of Docetaxel seemed to have a strong influence on efficacy in combined therapies. The individual strength of Tamoxifen was found to be a good factor in efficacy in combined therapies; however, it is limited by breast cancer type. According to Yan et al. [14], patients used Tamoxifen as prevention of late recurrence among metastatic breast cancer patients. Its usage as adjuvant to prevent Hormone Receptor (HR)-positive breast cancer has been producing promising results.

Recommendation

Single treatment clinical trials and randomized clinical trials with double treatment arms are commonly used for combined cancer therapies. However, using three treatment arms in clinical trials will reduce bias in the evaluation of efficacy and the analysis of safety with combined therapies. Three treatment arms treatments clinical trials will provide better evaluation of clinical efficacy among treatment groups of the drug of interest only, the other combined drugs only, and the combined therapy of drug of interest and other combined drug. According to Klijn et al. [10], three treatment arms will drive objective scientific evaluation on the cancer-combined therapies.

In addition, the combined therapies of both Docetaxel and Tamoxifen with each other, not with other drugs, in clinical trials may yield better results. One of such clinical trials is the GEPARDO (German Preoperative Adriamycin Docetaxel) trial, which had good result of effective breast-conserving surgery and pCR rates for two treatment arms of 122 patients receiving doxorubicin and docetaxel, and 128 patients receiving doxorubicin, docetaxel and tamoxifen [15]. However, the combined therapies of only Docetaxel and Tamoxifen with a large patient population may offer a better pathway for effective cancer therapies for all breast cancer types.

Conclusions

Combined therapies of Docetaxel and Tamoxifen have produced some level of efficacy, in term of tolerability and overall survival improvement, among targeted breast cancer patients. In the combined therapies of Docetaxel and Tamoxifen among female breast cancer, based on objective patient-based endpoint, OSR, median OSR was found to be slightly better in Docetaxel combined therapy than Tamoxifen combined therapy. OSR endpoint was used for the evaluation because it has the highest medical relevance to patients, and it has been observed as best efficacy assessment of cancer drug treatments [16].

The significance of this evaluation is embedded in the importance of individual strength of Docetaxel and Tamoxifen in their combined therapies, as well as the selection of the combined drugs used in their combined therapies. Docetaxel seems to possess better individual strength in its combined therapies because of its better drug interaction, and effective management with many breast cancer types than Tamoxifen. However, the superiority in overall survival result of Docetaxel over Tamoxifen in their combined therapies is negated by considerable number of safety issues experienced by the clinical trial subjects during clinical trial evaluation of combined therapies of both drugs. In addition, the combined drugs used in each of Docetaxel and Tamoxifen combined therapies should be well researched to possess capabilities to manage resistance, boost efficacy, and reduce toxicities of Docetaxel and Tamoxifen in their combined therapies.

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