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ARTICLE

Adjuvant Therapy of Breast Cancer with Docetaxel-Containing Combination (TAC) – A Hungarian experience in the BCIRG 001 trial

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The adjuvant chemotherapy of breast cancer changed in the past two decades. Docetaxel containing regimens are highly active in metastatic breast cancer. A logical approach was their incorporation into trials of early breast cancer adjuvant therapy. The authors present the Hungarian interim analysis and experience with the BCIRG 001 randomized, multicentric, phase III clinical trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) and FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer patients. The results are presented compared to the international data. Three Hungarian centers – Szt. Margit Hospital, Budapest, National Institute of Oncology, Budapest, Petz Aladár Hospital, Gyôr – participated in the international trial. Between June 1997 and June 1999, 61 patients with node positive breast cancer were enrolled in the study after the surgery. Thirty-four patients were randomized to TAC (75/50/500 mg/m^2 6xq3wk) and 27 patients were randomized to FAC (500/50/500 mg/m^2 6x q3wk) chemotherapy, with prospective stratification by node (1-3, 4+). Patients with hormone receptor positive tumors received tamoxifen for 5 years after the chemotherapy. Radiotherapy was performed after the 6th cycle of chemotherapy. 33 months of follow up was performed. In both arms the hematological toxicity was more frequent. The TAC group showed a higher incidence of neutropenia (76%) compared to the FAC (22%), as well as a higher incidence of febrile neutropenia (26 % versus none), without grade 3-4 infection and there was no cases of septic death. More grade 3-4 nausea and vomiting was observed in the FAC group. At three years follow up, results indicated improvement in disease-free survival (88% vs. 76%) in favour of TAC, and similar tendency was observed in the case of overall survival (97% vs. 88%). Based on the international data analysis TAC was superior to FAC chemotherapy, the results show statistically significant differences between the two arms. This benefit with TAC was seen regardless of hormone receptor status. Additional follow up data will evaluate the role of TAC in the adjuvant setting of early breast cancer treatment. (Pathology Oncology Research Vol 9, No 3, 166–169)

Keywords: early breast cancer, adjuvant chemotherapy, comparative study, docetaxel

Introduction

Adjuvant chemotherapy plays a significant role in improving survival of most women with early stage breast cancer, regardless of nodal, menopausal, or hormone receptor status.[1,7] The sequential combination of adjuvant chemotherapy and hormonal treatment for hormone receptor positive patients, appears more effective than either modality alone suggesting that they are complementary rather than competing options.[7,8] The wider use of screening mammography changed the stage distribution of breast cancers (BC), with more now being both smaller and of lower stage. Due to the data of randomized clinical studies adjuvant therapy of BC changed in the past two decades.[3] Adjuvant therapy of BC is based on recommandations of the St. Gallen consensus conferences and Oxford meta- analyses.[7,11] Cytotoxic therapy is the only proven effective systemic adjuvant therapy for patients

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with hormone receptor negative BC. Oxford overview meta-analyses in 1995 and 2000 demonstrated that anthracycline-based polychemotherapy confers a survival advantage over adjuvant Cyclophosphamide, Methotrexate, 5-Fluorouracil (CMF).[6,7] These studies revealed that the 6 cycles of FAC or FEC is more effective than the 6 cycles of classical oral CMF or the 4 cycle of Doxorubicine, Cyclophosphamide (AC).[7]

The taxanes (docetaxel, paclitaxel) are under investigation in the adjuvant setting in clinical trials because of their proven efficacy in metastatic breast cancer (MBC). Docetaxel (Taxotere) achieved an overall response rate in phase II studies of 61% when used as first- line therapy[2,5] and of 43% when used as second- line treatment.[10] Docetaxel polychemotherapy (AT and TAC) was proved to be the most effective.[12,16] Docetaxel containing regimens are highly active in MBC,[9] improving outcome in patient who have also failed anthracyclines or CMF, as well as in the first- line treatment of MBC.[4,12,15] The incorporation of Docetaxel into an anthracycline- based regimen for the adjuvant treatment of node- positive BC represented a logical progression.

Preliminary data of the first multicentric, multinational phase III trial on adjuvant treatment – BCIRG 001- designed to assess the relative effectiveness of a Docetaxel- based combination regimen (with Doxorubicine and Cylophosphamide) was recently published.[13] Selection of anthracycline combination was justified by those studies which indicated that 4 cycles of 2 drug anthracycline combination (AC or EC) is equally efficient compared to 6 cycles of CMF and 6 cycles of 3 drug anthracycline polychemotherapy (FAC or FEC) is superior over 6 cycle of CMF. FAC therapy was chosen as control since it is widely used for the postoperative treatment of high risk BC patients. In the TAC study of metastatic breast cancer the incidence of febrile neutropenia was 34% therefore in the BCIRG 001 study G-CSF administration was recommended only after developing febrile neutropenia.

Materials and Methods

Eligible patients with operable BC and positive lymph nodes (at least 6 nodes analysed) were randomized to receive adjuvant treatment with TAC or FAC. The patients were randomized within 60 days of definitive surgery. Patients were to be of good general health, with an age less than 70 years, a Karnofsky Performance Status greater or equal to 80%, and normal hematologic, hepatic, renal and cardiac function. All of them gave written informed consent. Patients received intravenous infusion of TAC (75 mg/m^2 Taxotere + 50 mg/m^2 Adriamycin + 500 mg/m^2 Cyclophosphamide) or FAC (500 mg/m^2 5-Fluorouracil + 50 mg/m^2 Adriamycin + 500 mg/m^2 Cyclophosphamide) chemotherapy. The cycles were repeated every 3 weeks, for up to 6 cycles.

Doxorubicine was administered first as 15 minute i.v. infusion followed by a 15 minute iv bolus 5-Fluorouracil and a 1 to 5 minute iv bolus Cyclophosphamide in the FAC group. Patients in the TAC group received Doxorubicine first as a 15 minute iv infusion, followed by a 1 to 5 minutes iv bolus Cyclophosphamide. Docetaxel was given as a 1-hour iv infusion, beginning 1 hour after the end of the Adriamycin administration. To reduce the risk of acute hypersensitivity reactions in the TAC arm, patients received dexamethasone 8 mg po (2x8mg, 6 doses). Five days after TAC chemotherapy a 10 days prophylactic ciprofloxacin administration was performed. Patients who developed febrile neutropenia in the TAC arm could receive G-CSF with subsequent cycles. Toxicity were evaluated based on the WHO criteria.

In case of hormone receptor (estrogen or progesterone) positive tumors patients were treated with Tamoxifen 20 mg/day for 5 years. Tamoxifen was begun 3-4 week after completion of the last cycle of chemotherapy. Ovarian ablation with LH-RH analog was allowed. After breast

Table 1. **Patients Characteristics**

Patients (n=61)	*TAC n=34*	*FAC n=27*
Median age(y)	54,5	51
Karnofsky	100%	100%
Premenopausal	53%	37%
Mastectomy	41%	44%
Radiotherapy	68%	67%
Tamoxifen	53%	37%

Table 2. **Tumor Characteristics**

Patients (n=61)	*TAC n=34*	*FAC n=27*
Nodal Status	%	%
1–3	44	37
4–10	44	56
>10	12	7
Tumor size, (cm)		
≤2	38	33
>2 és ≤5	59	67
>5	3	0
ER and / or PR +	62	45

Table 3. **Hematologic Toxicity**

Patients (n=61)	*TAC 34%*	*FAC 27%*
ANC <1000	76	22
Febrile neutropenia	26	0
Infection (Gr. 3–4)	0	0
Septic death	0	0
Anaemia (Gr. 3–4)	3	0
Thrombocytopenia (Gr. 3–4)	0	0

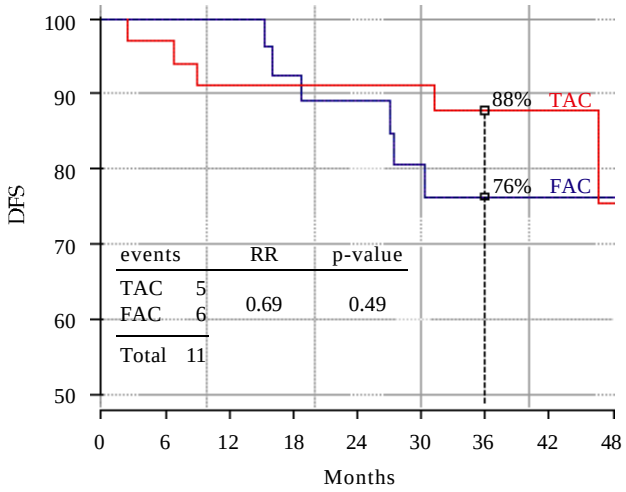
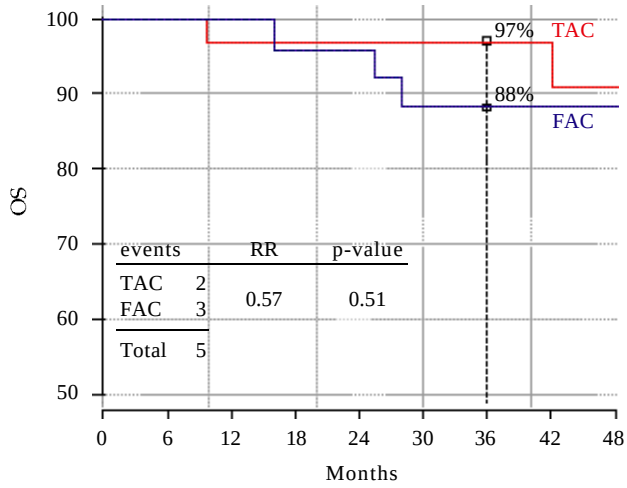


Figure 1. Comparison of the 33 months DFS (disease free survival) probability in BC patients treated according to TAC or FAC protocols. Data were analysed by Kaplan-Meier method. TAC (n=34), FAC (n=27).



Figures 2. Comparison of the 33 months OS (overal survival) probability in BC patients treated according to TAC or FAC protocols. Data were analysed by Kaplan-Meier method. TAC (n=34), FAC (n=27).

conserving surgery radiotherapy was mandatory. Following mastectomy radiotherapy was performed according the relevant protocols. Probability of survival was calculated by Kaplan- Meier method and considered significant when the p- value was less than 0.05.

Results

In the Hungarian centers a total of 61 patients were treated, 34 received TAC and 27 received FAC chemotherapy. Nearly all of these patients completed 6 cycles of chemotherapy (96% on FAC, 88% on TAC). Patients and tumor characteristics are summarized on *Table 1. and 2*. In both arms the hematologic toxicity was characteristic.

In the TAC group more patients experienced grade 3-4 neutropenia (76%), febrile neutropenia (76%) and grade 3-4 anemia. Febrile neutropenia did not result in infections, and there were no cases of septic death (*Table 3*). Non-hematologic toxicities characteristic for Docetaxel (allergy, edema, neuropathy, nail alterations) were rare.

Thirty-three month follow up of the patients allowed us to analyse the disease- free survival (DFS) and overall survival (OS) data of the trial. Disease free survival of patients in the TAC arm was 88% compared to 76% in the FAC group (*Figure 1*). This difference in favour of TAC chemotherapy was also maintained in the overall survival: 97% versus 88% respectively (*Figure 2*). Meanwhile these differences did not prove to be statistically significant due to the relatively low number of patients in each group.

Discussion

Comparison of the Hungarian BCIRG 001 and the global BCIRG 001 data on the side effects indicated a significantly increased afebrile and febrile neutropenia, and anemia in the TAC group.[13] Despite higher rates of febrile neutropenia through careful management there was no increased incidence of infection, and there were no septic deaths in either treatment arm of the trial. Both treatments were generally well tolerated, without any unexpected toxicities. Furthermore, nonhematologic toxicities were generally manageable on both arms. At the first planned interim analysis data based on the Hungarian and the global experience of the BCIRG 001 trial both indicated that adjuvant TAC treatment is significantly superior over FAC concerning the 33 month DFS and OS parameters.[13] Detailed analysis of the international data of BCIRG 001 proved that the DFS and OS benefit with TAC was greatest for patients with 1-3 positive nodes. The retrospective analysis showed that apparently no benefit in the 10+ node positive patients, the patients with 4-9 positive nodes do receive benefit with TAC.[13] On the other hand the superiority of the TAC chemotherapy over FAC is independent of hormone receptor and HER2/neu status of the tumors.[13] Further follow up of the patients involved in BCIRG 001 trial is necessary to confirm the role of TAC regimen in the adjuvant treatment of node positive breast cancer.

However, several questions are still open concerning the docetaxel therapy such as optimalization of the combination with other cytotoxics, optimal route of delivery, cycle duration, etc.[14] Meanwhile it can be predicted that the golden standard of adjuvant chemotherapy of early breast cancer will based on taxanes. The first agent developed on the basis of understanding of the biology of breast cancer, trastuzumab, has appeared in the clinic for the treatment of the tumors with HER/2 neu amplification. Probably an

other systemic adjuvant regimen will based on trastuzumab in the future. Results of ongoing adjuvant clinical trials will establish the role of taxanes and trastuzumab in the management of breast cancer and evaluate the real impact of them on the natural history of the disease.

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