

TAXANES IN ADJUVANT BREAST CANCER TREATMENT

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Abstract

Taxanes are irreplaceable drugs in treatment of many solid malignancies. In breast cancer they represent the backbone of adjuvant therapy and are important option in treatment of advanced and metastatic disease. Since their discovery in 1960's they went through a long journey of clinical development and positioning in clinical practise of treatment of early breast cancer. Taxanes belong to the fourth group of cytotoxic drugs, which act as mytotic inhibitors, causing the death of the cell in metaphase. Clinical trials conducted in patients with breast cancer evaluated different combinations of other chemotherapeutics with taxanes, different modes of administration, effectiveness of different chemotherapy regimens including taxanes in different subtypes and stages of the disease and effectiveness of individual taxanes in comparison with one another. Based on the results of those trials, today the relevant global oncology associations recommend the use of taxanes in treatment of early breast cancer, pointing out their significant benefit in total reduction of breast cancer mortality and risk of disease recurrence by 20-30% comparing to anthracycline only protocols. The purpose of this literature review was to provide comprehensive information about development of taxanes and their position in routine everyday clinical practise.

KEY WORDS: *taxanes, mytotic inhibitors, cytotoxic drugs, chemotherapy regimens, early breast cancer*

TAKSANI U LIJEČENJU RANOG RAKA DOJKE

Sažetak

Taksani su nezamjenjivi lijekovi u liječenju mnogih solidnih tumora. U karcinomu dojke predstavljaju okosnicu adjuvantne terapije i važna su opcija u liječenju uznapredovale i metastatske bolesti. Od njihovog otkrića 1960-ih prošli su dugi put kliničkog razvoja i pozicioniranja u kliničkoj praksi liječenja ranog raka dojke. Taksani pripadaju četvrtoj skupini citotoksičnih lijekova koji djeluju kao inhibitori mitoze, koji uzrokuju smrt stanice u metafazi. Klinička istraživanja provedena na bolesnicama s karcinomom dojke procjenjivala su različite kombinacije drugih kemoterapeutika s taksanima, različite načine primjene, djelotvornost različitih kemoterapijskih protokola koji uključuju taksane u različitim podtipovima i stadijima bolesti te učinkovitosti pojedinih taksana u usporedbi s drugim. Na temelju rezultata tih pokusa, danas relevantne globalne onkološke udruge preporučuju uporabu taksana u liječenju ranog raka dojke, pokazujući njihovu značajnu korist u ukupnom smanjenju rizika od smrti i povrata bolesti za 20-30% u odnosu na protokole bazirane samo na antraciklinu. Svrha ovog pregleda literature je pružanje sveobuhvatne informacije o razvoju taksana i njihove pozicije u rutinskoj svakodnevnoj kliničkoj praksi.

KLJUČNE RIJEČI: *taksani, mitotički inhibitori, citotoksični lijekovi, kemoterapijski režimi, rani rak dojke*

INTRODUCTION

Various forms of systemic antineoplastic treatment are used in the adjuvant treatment of early breast cancer: chemotherapy, endocrine therapy and targeted therapy, depending on the stage of the disease, biological characteristics of the tumor, as well as the characteristics of the patient himself. The decision on the optimal form of systemic antineoplastic treatment is made by a multidisciplinary team. The backbone of adjuvant chemotherapy in the treatment of early and advanced non-metastatic breast cancer consists of two groups of cytotoxic drugs, anthracyclines and taxanes. Oxford meta-analysis from 2005 (EBCTCG – Early Breast Cancer Trialists' Collaborative Group), which included 194 studies with more than 145 000 patients, showed that by using anthracycline-containing adjuvant polychemotherapy, the risk of mortality decreased by 38% in patients under the age of 50 and by 20% in the group from 50 to 69 years of age, which clearly confirmed the position of anthracyclines as the gold standard in adjuvant treatment of breast cancer in patients under 70 (1).

However, anthracycline efficacy in treating cancer is limited by a cumulative dose-dependent cardiotoxicity (recommended cumulative maximum of doxorubicin is 450 mg/m²), which can cause irreversible heart failure. The cardiotoxicity is mediated by cellular mechanisms, responsible for increased apoptosis in cardiac myocytes. This can cause irreversible structural changes which is especially important to keep in mind when treating population of potentially curable patients so patients should be closely monitored during the adjuvant treatment. This problem was one of the reasons investigators push forward to find another drug alternative in this setting (2).

Taxanes have been known since the 1960's, after paclitaxel was isolated from pacific yew as a part of the NCI (National Cancer Institute) experiment, which examined the characteristics of a large number of different trees. Given the non-viability of raw material consumption, relative to the amount of compound obtained, a semi-synthetic method of obtaining paclitaxel was developed. The clinical course of drug development was slow. In 1987 paclitaxel was introduced to treat ovarian cancer, breast and lung tumors. In the 1980's docetaxel was synthesised and it has been used in breast cancer therapy since the 1990's (3).

Taxanes belong to the fourth group of cytotoxic drugs, which act as mitotic inhibitors. They are inhibitors of mitosis of the spindle fibers in the cell and cause a 'mitotic block' at the transition from metaphase to anaphase of the cell cycle. They are responsible for binding to microtubules, resistance to depolymerization of the resulting polymers, generation of defective microtubules and the death of the cell in metaphase. Comparison of taxanes showed that docetaxel has a higher affinity for microtubules, achieves better translocation in the cell, has slower release from the tumor cell, induces polymerization stronger and is more potent than paclitaxel. It has 12 times stronger cytotoxic activity than paclitaxel. In preclinical studies, docetaxel showed widespread activity in the cell cycle (4,5).

The most pronounced side-effect of taxanes therapy noted in clinical studies and in clinical practise is neutropenia which can reach high grade in up to 80% of patients treated with docetaxel and about 10% of patients develop febrile neutropenia (this effect is less common with paclitaxel and least common with nab-paclitaxel). Also important and dose limiting side-effect of therapy is peripheral neuropathy which occurs in high grade in about 10% of patients. Less frequent side-effects include anemia, vomiting, stomatitis and edema (6).

Addition of taxanes improves results of adjuvant therapy

Taxanes have been used in breast cancer therapy since the 1990s. Their activity was first tested in advanced disease studies and then in adjuvant use in early and advanced non-metastatic breast cancer. The *American Food and Drug Administration* (FDA) approved the use of paclitaxel in the treatment of metastatic breast cancer in 1994. Approval was obtained based on a phase III study which compared two doses of paclitaxel (175 mg/m² and 135 mg/m² every three weeks) in patients who did not respond to prior chemotherapy. It has been shown that higher doses of paclitaxel have achieved longer median time to progression of the disease (TTP), longer median overall survival (OS), and longer median survival over 6 months (7).

The development of targeted indications for the treatment of non-metastatic breast cancer with taxanes has begun with the first generation of randomized clinical trials investigating the addition

Table 1.

FIRST GENERATION OF CLINICAL TRIALS WITH TAXANES

Authors/Trial	No. of patients	Regimen	Results
Henderson et al./CALGB 9344	3,121 pts	AC (doxo 60/75/90 mg/m ²) 3w +/- paclitaxel 175 mg 3w	DFS 70% vs. 65% OS 80% vs. 77%
Mamounas et al./NSABP B-28	3,060 pts	AC vs. AC+paclitaxel	DFS 72% vs. 76% OS 85% vs. 85%
Roche et al./PACS 01	1,999 pts	FECx6 3w vs. FECx3+docetaxelx3 3w	DFS 73% vs. 78% OS 87% vs. 91%
GEICAM 9906	1,246 pts	FECx6 3w vs. FECx4 3w+paclitaxelx8 1w	DFS 72% vs. 78% OS 87% vs. 90%
BCIRG 001	1,491 pts	FACx6 3w vs. TACx6 3w	DFS 68% vs. 75% OS 81% vs. 87%

of taxane to anthracyclines, compared with the use of anthracycline only protocols. A large study by Henderson and associates, CALGB (Cancer And Leukemia Group B) 9344, on over 3, 000 breast cancer patients, showed that the addition of paclitaxel to anthracycline protocol (to the current standard treatment protocol of 4 x AC) provided a 17% reduction in the relative risk of disease recurrence, as well as 18% reduction in the relative risk of mortality. Clearly greater benefit has been shown in patients with hormone-independent disease. However, the CALGB 9344 study did not investigate the same duration of comparable chemotherapy protocols, so it positioned taxane chemotherapy as an alternative to prolonged anthracycline therapy (8). A very similar NSABP B-28 study by demonstrated that the addition of paclitaxel to anthracycline protocol significantly reduced the risk of recurrence, but did not prolong OS (90). According to a study PACS 01, by Roche et al., docetaxel administration after standard six-cycle FAC (5-fluorouracil, doxorubicin, cyclophosphamid) protocol, reduced risk of disease recurrence by 18%, with a total of 27% reduction in the risk of death (10). The study GEICAM (Spanish cooperative breast cancer research group) 9906 showed 23% reduction in risk of disease recurrence with the use of weekly paclitaxel after FEC (5-fluorouracil, epirubicin, cyclophosphamid), compared to the use of anthracyclines only (11). Study by Buzdar et al. confirmed that improved results, obtained in previous adjuvant anthracycline plus taxane studies, were undoubtedly caused by addition of taxanes to chemotherapy protocol, rather than the longer duration of adjuvant therapy when adding taxane (12). (Table 1.)

Two studies have relativized the role of taxane therapy in the adjuvant breast cancer treatment. UK TACT and smaller Albert et al. study showed no significant difference between DFS and OS between group of patients treated with anthracycline-based polychemotherapy only and patients treated with antracycline plus taxane (13,14).

Concomitant use of taxanes and anthracyclines and taxanes without antracyclines

Studies that investigated combination of taxanes with doxorubicin, are two major studies, BCIRG (Breast Cancer International Research Group) 001 and E 2197. In the first study, the comparison of anthracycline protocols FAC and TAC (docetaxel + doxorubicin + cyclophosphamide) resulted in 28% reduction in risk of disease recurrence and 30% reduction in risk of death with TAC chemotherapy (15). (Table 1.) The mentioned five-year follow-up results were maintained after 10 years of follow-up (16). TAC also showed advantage in DFS compared to FAC in high-risk patients without metastases in the lymph nodes (19). Study E 2197 demonstrated, on 2 950 patients, after 53 months follow-up no statistically significant difference in DFS and OS between AT (doxorubicin + docetaxel) and AC (doxorubicin + cyclophosphamide) protocol, with both protocols showing unexpectedly good results, although doubtfully sub-optimal dose of docetaxel was applied (17).

USO 9735 demonstrated the advantage of using taxanes without anthracyclines (comparison of TC to AC protocol). After seven years of follow-up, TC protocol showed the advantage in DFS and

OS in both older and younger patients, and the advantage was more pronounced with longer follow-up, positioning the TC protocol as a standard of non-anthracycline protocols (18).

Data from meta-analysis

In order to determine the role of taxanes in adjuvant breast cancer treatment, Cochrane metaanalysis was performed on 21 000 patients in 12 studies. The analysis included patients with operable disease, stage I - III. Use of taxanes provided statistically significant prolongation of disease-free survival (DFS) and overall survival (OS). However, subgroup of patients that would have the highest benefit of taxane therapy was not identified, so it is recommended that all patients with stage I disease should be considered for adjuvant therapy. In patients with lymph node involvement, adjuvant chemotherapy including taxanes showed a DFS prolongation of 24% and OS prolongation of 15%, compared to adjuvant non-taxane treatment. Proportionally achieved risk reduction was the same in patients with and without lymph node involvement. The greatest benefit of chemotherapy has been shown in patients under the age of 50, and data were missing for those older than 70 years. This metaanalysis has led to the conclusion that the addition of taxanes to adjuvant chemotherapy increases its effectiveness, regardless of age, nodal status, tumor size and stage, and hormone receptor expression. The preferred mode of administration is sequential over the concomitant (20).

In 2012, the data from the before mentioned EBCTCG metaanalysis from 2005 were updated. More than 40 000 patients, treated with the protocol including taxanes, were involved in the study. The parameters that have influenced the reduction of recurrence and mortality risk were anew considered. In the context of taxane appliance, the results showed that the use of taxanes in any combination gave better results than disuse and that prolonged treatment yielded better results compared to earlier interruption of therapy, but with the risk of cumulative toxicity, and polychemotherapy protocols yielded better results compared to monochemotherapy. Overall, adjuvant chemotherapy based on anthracyclines and taxanes has shown a 1/3 reduction in breast cancer mortality compared to observation (21).

Weekly paclitaxel - an option of choice

The second generation of adjuvant randomized clinical trials compared different regimens using taxanes, the differences between sequential and concomitant (combination) use and the differences between dose dense and standard (three-week) applications. The CALGB C9741 study compared, on 2 000 patients, four paclitaxel regimens; standard sequential application after AC regimen and single sequential A>P>C regimen in two-week (dose dense) or three-week intervals. After 36 months of monitoring, the two-week paclitaxel regimen showed a significant advantage in DFS and OS, but after 69 months, the difference in OS disappeared. There was no difference between the sequential drug administration and the standard AC-taxane sequence (22). In the BIG 2-98 study, involving 2900 patients, the difference between sequential and concurrent administration of docetaxel with doxorubicin was investigated. The comparison showed the advantage of the sequence A>T>CMF in comparison to A>CMF, but the same advantage was not observed in AT>CMF when compared to A>CMF. After ten years of follow-up, the DFS was not significantly prolonged in the case of anthracycline-taxane sequence as it was in earlier follow-up, but docetaxel showed and maintained significant benefit in high-risk ER (estrogen receptors) dependent patients (23).

In the study by Shulman et al., comparing three protocols, AC>T, TAC and AT, the standard sequence AC>T showed significantly better DFS than TAC and AT, but not significantly better OS. AT was shown not to be inferior to TAC, thus additionally narrowing the indication area for the highly toxic TAC protocol (24).

The comparison of taxane based chemotherapy was performed in a large study by Sparano et al., E 1199 which included 4 954 breast cancer patients. Study compared paclitaxel and docetaxel in weekly versus three-week regimen in sequential application after standard four-cycle anthracycline (AC) therapy. After 63,8 months of follow-up, the benefit of the weekly paclitaxel and three-week docetaxel over three-week paclitaxel, has been shown. Weekly paclitaxel showed an advantage in DFS and OS (docetaxel only in DFS), in patients with positive hormone receptors, as well as in Her2 negative patients. This made the paclitaxel weekly

regimen an option of choice (25). The SWOG 221 study on 2 700 patients showed, after six years of follow-up, that low dose weekly paclitaxel (80mg/m² for 12 weeks) was as effective as dose-dense paclitaxel (175mg/m² every two weeks, supported by granulocyte colonies growth factors) but significantly less toxic (26). A small stage II study of Burkard et al., compared standard docetaxel (4xTC every three weeks) with dose dense application (4xTC every two weeks), supported by granulocyte colonies growth factors. Both regimens have shown a similar profile of toxicity and tolerability (27). Further research results are expected. A study by a group of authors from Greece in 2014 showed similar results in DFS between dose dense administration of paclitaxel and docetaxel, following the anthracycline protocol (4xFEC) in patients with involved lymph nodes, but because of the more acceptable toxicity profile, paclitaxel has been confirmed as a taxane of choice (28).

Taxanes in HER2 positive disease

In HER2 positive breast cancer, which accounts for about 20% of all breast cancers, patients have greater risk of disease relaps and death from metastatic disease. In this subgroup of patients several studies have positioned taxanes as standard of treatment in combination with trastuzumab immunotherapy (29,30,31). A small, uncontrolled single center study (the so-called APT study) by Tolaney et al., performed on 406 low-volume tumor patients without affected lymph nodes, showed 93.3% DFS and 95% OS after 7 years of follow-up, with the combination of weekly paclitaxel with trastuzumab followed by trastuzumab up to one year of therapy. This study has shown that, in localized small HER2 positive tumors, it is possible to avoid administration of anthracyclines in adjuvant treatment (32). Jones and colleagues study showed good results with four cycles of TCH, followed by trastuzumab up to a total of one year of treatment in patients with lower risk disease (33) and Perez et al. demonstrated the advantage of concomitant application of trastuzumab with taxanes versus sequential treatment (34).

DISCUSSION

With the review of historical development of targeted indications for use of taxanes, as well as

the positioning of these drugs in breast cancer treatment, several important points of reference were made. The major studies, such as the CALGB 9344, PACS 01 and BCIRG 001 set taxanes to the basis of adjuvant breast cancer therapy. Then there were studies which raised doubts about the advantage of introduction of taxanes with former anthracycline treatment standards and urged to seek additional confirmation through new research, such as the studies NCIC CTG MA 21.1 and the UK TACT. A series of meta-analysis clearly showed the benefit of introducing taxanes. Study E 1199 confirmed the importance of the mode and the regimen of administration itself and defined weekly paclitaxel and three-week docetaxel as the regimens of choice. There were no clear differences or advantages of one of the taxanes over the other. A TC protocol was established as a standard non- anthracycline protocol for older and cardiovascular patients. Excellent results were obtained in the treatment of small Her2 positive tumors with a combination of taxane and targeted therapy, without previous anthracycline chemotherapy. An advantage of the dose-dense application regimens has been demonstrated over the standard three-week-apart applications.

From the first confirmation of the role of taxanes to date, there were no revolutionary innovations or changes in the adjuvant treatment of breast cancer, but the progress in optimizing the dose and regimen of administration is evident. Significant improvement in rate of complete pathological responses and DFS was reported in neoadjuvant treatment with nab-paclitaxel (nanoparticle *albumin-bound paclitaxel*) in comparison with conventional paclitaxel (35). Further investigations with this form of drug in adjuvant setting are ongoing.

Today, the most important global oncology associations, the *American National Comprehensive Cancer Network* (NCCN) and the *European Society for Medical Oncology* (ESMO) clearly point out the role of taxanes added to anthracycline chemotherapy in total reduction of mortality risk by 1/3 and in improving adjuvant breast cancer treatment, with less pronounced cardiac toxicity. They recommend the sequential administration of taxanes after anthracycline regimen and the use of weekly paclitaxel and three-weekly docetaxel as the best choice.

Issues that remain open for future discussion are numerous indications for off label use of taxane therapy, which could serve as a model for new

opportunities in the use of these drugs, the issue of treatment duration in metastatic disease and management of side effects, the issue of combination of taxanes with other cytotoxic drugs and targeted therapies, as well as the issue of new formulations of these drugs.

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