

# PCN13 COST-EFFECTIVENESS ANALYSIS OF DOCETAXEL VERSUS OTHER REGIMENS IN THE ADJUVANT THERAPY OF EARLY AND LOCALLY ADVANCED BREAST CANCER IN POLAND

Walczak J<sup>1</sup>, Pawlik D<sup>1</sup>, Wojcik R<sup>1</sup>, Kaczor M<sup>1</sup>, Lis J<sup>2</sup>, Nogas G<sup>1</sup>

<sup>1</sup>Arcana Institute, Cracow, Poland, <sup>2</sup>Sanofi-Aventis, Warsaw, Poland

## BACKGROUND:

Breast cancer is the leading cause of cancer death of women in Poland. Neoadjuvant, or preoperative, chemotherapy is used in the management of patients with locally advanced or large primary breast cancers. The aims of the treatment are to reduce the primary tumor size allowing breast conservation surgery and to improve overall survival by destroying micrometastases. Anthracycline-based chemotherapies are still used as standard regimens for the neoadjuvant treatment. Docetaxel (Taxotere) is established as one of the most effective chemotherapeutic agents in the treatment of breast cancer, being evaluated also in other solid tumours (lung, gastro-oesophageal, ovarian and prostate cancers). Randomized controlled trials involving neoadjuvant treatment found that chemotherapy with a regimen that includes docetaxel significantly improves pathological response, BCT rates and overall survival compared with anthracycline based chemotherapy among women with locally advanced or large primary breast cancer.

## OBJECTIVES:

The aim of this analysis was to assess the cost effectiveness of neoadjuvant chemotherapy with docetaxel compared to standard anthracycline-based regimens in the treatment of locally advanced breast cancer.

## MATERIALS AND METHODS:

Lifetime Markov model was developed to investigate the cost-effectiveness of using docetaxel regimens in place of anthracycline-based chemotherapy in neoadjuvant treatment of locally advanced breast cancer. Clinical data from published, randomized controlled trials and Polish cost data were used.

In the primary analysis the cost effectiveness of sequential therapy CVAP+T compared with CVAP alone was assessed, based on the Aberdeen trial. Additionally, next three comparisons were performed (AC+T vs AC, AT vs AC, AT vs FAC) using survival data from the CVAP+T vs CVAP trial (assuming equality of survival in all analysed taxane-based groups and equality of survival in all anthracycline-based but non-taxane therapies) and other clinical data from head-to-head RCTs.

The incremental cost effectiveness ratios, expressing the cost per life year gained due to use of regimen containing docetaxel instead of a standard chemotherapy for the treatment, were calculated.

The perspective of health care payers (budget of the National Health Fund and patient) and a lifetime horizon was considered.

Direct medical costs: cost of initial chemotherapies (drugs and administration), tamoxifen, severe (grade III/IV) adverse events, radiotherapy or mastectomy (in case of local recurrence) and further chemotherapy (in case of distant metastases) were taken into account.

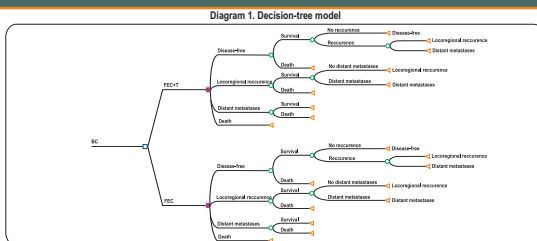
## MODEL STRUCTURE:

Based on the Aberdeen trial, a lifetime Markov model was developed to investigate the cost-effectiveness of using docetaxel in monotherapy in place of CVAP regimen after 4 cycles of CVAP chemotherapy in neoadjuvant treatment of locally advanced breast cancer. The target population were patients with newly diagnosed large or locally advanced breast cancer.

Additionally, cost effectiveness analyses of AC+T vs AC, AT vs FAC and AT vs AC were performed assuming that survival in all docetaxel groups (AC+T, AT, CVAP+T) is the same (survival was assessed only in the Aberdeen trial) and survival in all groups receiving anthracycline-based regimens (AC, CVAP, FAC) is also equal. The four states defined in the models were:

- neoadjuvant/surgery – the initial state
- after BCT – women who received breast conserving treatment after neoadjuvant chemotherapy
- after mastectomy – patients treated with mastectomy after neoadjuvant chemotherapy
- death – the absorbing (terminal) state.

Model design is presented on the following diagram (example for CVAP+T vs CVAP comparison).



## COSTS (CVAP+T vs CVAP):

Direct medical costs were included: cost of chemotherapy, primary surgery (mastectomy or breast conserving treatment) and severe (grade III/IV) adverse events.

### Chemotherapy

Drug costs were based on the protocol doses stated in Aberdeen trial and local unit costs. All patients received four cycles of CVAP (1000 mg/m<sup>2</sup> of cyclophosphamide; 1,5-2 mg/m<sup>2</sup> of vincristine; 50 mg/m<sup>2</sup> of doxorubicin; 40 mg/day × 5 of prednisolone) every three weeks prior to surgery. Patients experiencing response were then randomized to receive:

- Four additional cycles of CVAP (with a higher prednisolone dose of 100 mg/day × 5), or
- Four cycles of docetaxel (100 mg/m<sup>2</sup>) every three weeks plus 100 mg/day × 5 of prednisolone.

Adjuvant therapy was not given after surgery. All patients received intravenous dexamethasone as premedication and this cost was not included in the analysis. Cost of hospitalization for chemotherapy administration was not taken into account assuming that it's equal in both groups and therefore has no impact on incremental analysis results.

The unit cost of Taxotere is 43,42 PLN/1 mg of docetaxel. Unit costs of other chemotherapeutics were taken from Polish National Health Fund's list of reimbursed medical services or Polish pharmacies (source: Wykaz Leków Refundowanych nr I/2005).

### Model parameters

The model parameters are presented in table 1.

Calculated costs are incurred in the first model „cycle” They include cost of neoadjuvant chemotherapies, adverse events, cost of surgery (with cost of radiotherapy after BCT).

Rates of patients with BCT after neoadjuvant chemotherapy confirm benefits from applying docetaxel: 67% patients from docetaxel group and only 48% patients from CVAP group could have performed lumpectomy (based on Aberdeen study). The difference is statistically significant favours docetaxel (p < 0,01).

Utility values for the lumpectomy and mastectomy state were extracted from the study Norum et al. „Lumpectomy or mastectomy? Is breast conserving surgery too expensive?” (Breast Cancer Research & Treatment 45; 7-14, 1997). Estimations (based on EuroQol questionnaire) were 0,87 and 0,84 for BCT and mastectomy, respectively. It should be noted that these utility scores are assumed constant over time in the model, therefore no adjustment in quality of life to further risk of disease is taken into account.

Table 1. Model parameters

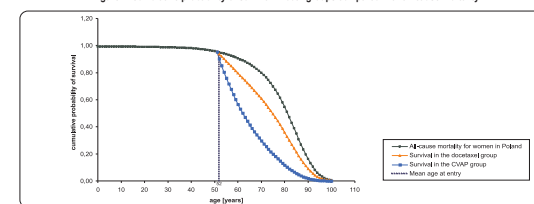
Parameter (95% CI)	CVAP + Docetaxel	CVAP
Drugs cost [PLN]	31 164,10	3 175,08
Lumpectomy cost [PLN]		3 000
Radiotherapy (following BCT) cost [PLN]		5 000
Mastectomy cost [PLN]		3 200
Cost of adverse events managing [PLN]	2 700	3 200
Probability of undergoing lumpectomy	0,67	0,48
Probability of undergoing mastectomy	0,33	0,52
Utility for the state: after BCT	0,87	
Utility for the state: after mastectomy	0,84	
Survival rate in subsequent cycles (years)	Varies over time	

## Transition probabilities

One cycle of the model represented 12 months. The mean age of patients entering the model was assumed to be 53, as in the Aberdeen trial. Transition probabilities of survival were derived from the Aberdeen trial. Using time-to-event data (3 and 5-year OS) for both groups, the exponential survival function defined as  $\exp(-\lambda t)$  was fitted, and hazard ( $\lambda$ ) calculated ( $\lambda_{tax} = 0,0142$ ,  $\lambda_{cvap} = 0,0504$ ). This excess mortality rate was then added to the all-cause mortality to obtain the time-dependent transition probabilities, which are (for age  $n$ ):  
 $tp_{(death)}_{tax} = tp_{(death)}_{all-cause} + \lambda_{tax}$   
 $tp_{(death)}_{cvap} = tp_{(death)}_{all-cause} + \lambda_{cvap}$   
 where  $tp_{(death)}_{all-cause}$  is the all-cause mortality for Polish women aged  $n$  years (source: GUS, 2004).

It should be noted that due to small number of patients in the Aberdeen trial (52 women in each group), mortality estimations based on this data should be viewed cautiously. This mortality rate was then added to the all-cause mortality to obtain the time-dependent transition probabilities.

Figure 2. Cumulative probability of survival in both groups compared with all-cause mortality



## RESULTS:

Table 2. Cost-utility analysis results for CVAP + T vs CVAP comparison

Neoadjuvant regimen	Cost per patient [PLN]	Incremental cost [PLN]	Quality-adjusted life years (QALY)	Incremental QALY	ICER [PLN/QALY]
CVAP	11 879,07		12,576		–
CVAP + Docetaxel	40 285,10	28 401,03	20,507	7,931	3 580,95

In table 2 the results of cost-utility analysis of CVAP + docetaxel vs CVAP comparison in the locally advanced breast cancer neoadjuvant treatment are presented.

The cost-utility analysis showed that neoadjuvant chemotherapy with CVAP and docetaxel is more expensive but also more effective compared with CVAP regimen. From the payers perspective (NHF and patient) the incremental cost effectiveness ratio was 3 580,95 PLN per quality adjusted life year gained.

### AC + T vs AC

Assuming that

- treatment effectiveness (overall survival) in the AC + T and CVAP + T groups are equal,
  - treatment effectiveness (overall survival) in the AC and CVAP groups are equal,
- neoadjuvant sequential chemotherapy with AC and docetaxel is more expensive but also more effective compared with AC regimen. From the payers perspective (NHF and patient) the incremental cost effectiveness ratio was 3 955,19 PLN per quality adjusted life year gained.

### AT vs AT

Assuming that

- treatment effectiveness (overall survival) in the AT and CVAP + T groups are equal,
  - treatment effectiveness (overall survival) in the AC and CVAP groups are equal,
- neoadjuvant chemotherapy with AT is more expensive but also more effective compared with AC regimen. From the payers perspective (NHF and patient) the incremental cost effectiveness ratio was 4 299,62 PLN per quality adjusted life year gained.

### AC vs AT

Assuming that

- treatment effectiveness (overall survival) in the AT and CVAP + T groups are equal,
  - treatment effectiveness (overall survival) in the FAC and CVAP groups are equal,
- neoadjuvant chemotherapy with AT is more expensive but also more effective compared with FAC regimen. From the payers perspective (NHF and patient) the incremental cost effectiveness ratio was 3 004,19 PLN per quality adjusted life year gained.

## SENSITIVITY ANALYSIS:

To compare neoadjuvant chemotherapy including docetaxel to other standard regimens in the treatment of breast cancer one way sensitivity analysis was performed. The following parameters were changed:

- utility value for the states: lumpectomy and mastectomy (based on Norum 1997 study, utility value for the lumpectomy state was assumed 0,90 and utility values for the mastectomy state was chosen equal to 0,85 and 0,80;
- probability of death (maximum and minimum of confidence interval for the risk);
- maximum and minimum rate of performing lumpectomy;
- cost of docetaxel (-10%, +10%);
- cost of medications composing CVAP, AC or FAC regimens;
- discount rates;
- cost of tamoxifen (-10%, +10%).

For every comparison of docetaxel group and control group the maximum ICER increase (27%) in relation to the baseline state was observed while assuming minimum survival probability in the docetaxel group and the maximum ICER decrease (17%) in relation to the baseline state was observed while assuming minimum survival probability in the control group.

### CVAP+T vs CVAP

Changes of utility value, cost of CVAP regimen and rate of lumpectomy procedures slightly modified the result obtained for based values of respective parameters.

### AC+T vs AC

Changes of discount rate, utility value, cost of tamoxifen and the rate of lumpectomy procedures slightly modified the result obtained for based values of respective parameters. Changing the cost of doxorubicin and cyclophosphamide didn't influence the incremental costs because the medications were applied in the same doses at the both groups.

### AT vs FAC

Changes of utility value, cost of FAC regimen and the rate of lumpectomy procedures slightly modified the result obtained in base-case analysis.

### AT vs AC

Changes of utility value, cost of doxorubicin and cyclophosphamide and the rate of BCT procedures slightly modified the result obtained in base-case analysis.

### Analysis limitations

The utility scores for states "After BCT" and "After mastectomy" are constant over time, therefore no further risk of disease is taken into account. Small population (N=52 for both groups) for which survival was assessed (Aberdeen trial). Assumption (for AC+T vs AC, AT vs FAC and AT vs AC comparisons) of equality in survival in all docetaxel groups and in all anthracycline groups.

## CONCLUSION:

Neoadjuvant chemotherapy containing docetaxel is a cost effective alternative to anthracycline-based regimens in the treatment of locally advanced breast cancer. ICERs per QALY are well below the acceptable threshold for cost-effectiveness in Poland.

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