

Cost effectiveness of adjuvant cyclophosphamide containing regimes to AT in the treatment of breast cancer in Germany

E. Walter^a, D. Mercsanits^a

^aIPF Institute for Pharmacoeconomic Research, Vienna, Austria

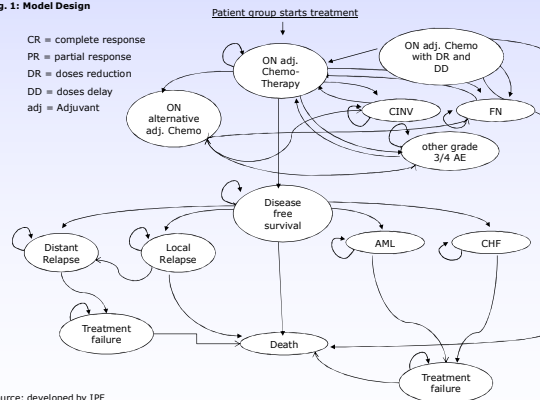
Objectives

As health economic data for well established adjuvant chemotherapy regimes in breast cancer patients like **anthracycline based regimes** rarely exists, this analysis addresses the cost-effectiveness of these treatment options **compared to a taxane-containing regime**. The combination of doxorubicin and cyclophosphamide (AC) has been a standard adjuvant breast cancer regime. The purpose of this analysis was to estimate the cost-effectiveness of AC, CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and FEC (5-fluorouracil, epirubicin and cyclophosphamide) compared with AT (doxorubicin and docetaxel) administered as adjuvant therapy to women with node-positive early breast cancer in Germany. Long-term costs and consequences have been evaluated (beyond DFS and OS from clinical trials) to highlight the value for money of the chosen comparators.

Methods

We developed a multi-country Cost-Utility-Model to simulate the long-term consequences from initiation of adjuvant chemotherapy over ten years. Markov-modeling techniques were used to estimate the incidence of complications during chemotherapy (febrile neutropenia, chemotherapy-induced nausea/vomiting, dose reduction, dose-delay, other grade 3/4 adverse-events) and long-term consequences like local or distant relapse, acute myelogenous leukemia, chronic heart failure and death. Monte-Carlo simulation accounted for uncertainty. The model comprises 14 health states, with a cycle length of 3 months. Transition probabilities were derived from clinical and epidemiological studies; direct costs (2011 Euro) from published sources. The present economic evaluation was conducted from the perspective of the health care system. The medical resource use was determined on the basis of literature research and was validated externally by experts. All costs were collected from official price lists. Utilities were derived from the published literature. QALYs, life-years and costs were discounted at 3% p.a.

Fig. 1: Model Design



Source: developed by IPF

Institute for Pharmacoeconomic Research
IPF
 Research

CONTACT:
 Dr. Evelyn Walter
 IPF Institute for Pharmacoeconomic Research
 Wollfengasse 4/7
 1010 Vienna, Austria
 Tel +43-1-5132007-13
 Fax +43-1-5132007-15
 Email: e.walter@ipf.at
 Web: www.ipf.at

Cohort definition

Patients with a mean age of 50 years entered the model after surgery and start with the adjuvant AT, AC, CMF or FEC chemotherapy. The cohort is defined as 1,000 women with primary operable breast cancer (mastectomy or breast-conserving surgery/lumpectomy), at least one histological verified positive axillary node. Included subgroups are: (A) triple negative patients, (B) estrogen receptor-positive patients and (C) progesterone receptor-positive patients. We assume that the patients' average weight is 60 kg and their body-surface area 1.6m².

Results

Adjuvant chemotherapy inclusive supportive therapy was associated with costs between 2,283.28 € (AC) and 6,736.76 € (FEC). Total costs including follow-up costs over a 10 year time horizon range from 17,018.04 € for AC to 21,055.91 € for AT. An overview of cost components is presented in Table 1.

Tab. 1: Total costs broken down by its costs components

Cost components	AT	AC	CMF	FEC
Adjuvant CT	5,241.22 €	2,283.28 €	2,628.09 €	6,736.76 €
Alternative CT and DR	18.41 €	41.09 €	48.68 €	43.47 €
Local relapse	655.85 €	580.53 €	547.74 €	394.06 €
Distant relapse	14,149.40 €	13,157.58 €	13,744.91 €	9,844.75 €
AML	902.17 €	815.34 €	801.43 €	1,322.45 €
CHF	88.86 €	140.22 €	19.58 €	130.35 €
Total	21,055.91 €	17,018.04 €	17,790.42 €	18,471.84 €

Source: IPF own calculations

AT resulted in a discounted quality-adjusted life expectancy of 6.3 years. The corresponding life expectancy without quality adjustment amounts to 7.0 life-years (LYs). AC shows comparable outcomes. The cost-saving potential associated with AC vs. AT amounts to 4,037.87 € per patient. Costs, QALYs and LYs associated with CMF are 17,790.42 €, 6.3 and 6.9 years. FEC associated total costs are 18,471.84 € and dominate AT and CMF. Quality-adjusted life expectancy increases to 6.5, which represents a QALY gain of 0.2 QALYs over 10 years. Life expectancy without quality adjustment amounts to 7.4 and leads to 0.34 LYs gained versus AT (see table 2).

All cyclophosphamide-containing regimes are associated to cost savings compared to AT.

Tab. 2: Results of costs QALYs and LYs

Strategy	Costs C	Diff. ΔC	QALYs E	Diff. QALYs ΔE	ICER
AT	21,055.91 €		6,3139		
AC	17,018.04 €	-4,037.87 €	6,3115	-0,0024	vs. AT 1.7 mill
CMF	17,790.42 €	-3,265.49 €	6,3030	-0,0109	vs. AT 0.30 mill
FEC	18,471.84 €	-2,584.07 €	6,5097	0,1958	FEC dominant vs. AT
Strategy	Costs C	Diff. ΔC	LYs E	Diff. LYs ΔE	C per LYs gained
AT	21,055.91 €		7,0186		
AC	17,018.04 €	-4,037.87 €	7,0014	-0,0172	vs. AT 0.23 mill
CMF	17,790.42 €	-3,265.49 €	6,9378	-0,0808	vs. AT 40k
FEC	18,471.84 €	-2,584.07 €	7,3619	0,3433	FEC dominant vs. AT

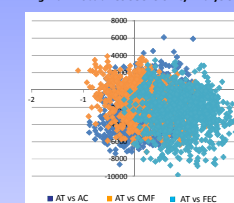
Source: IPF own calculations

ICER = incremental cost effectiveness ratio

Over a 10-year timeframe, AC, CMF and AT lead to fewer cases of AML: 1.75 per 100 patients vs. 2.8 when FEC is used. FEC leads to fewer cases of local and distant relapses: 10 local relapse per 100 patients vs. 15 (the three other treatments) and 15 distant leaps per 100 FEC treated patient vs. 21-23 with the three other treatments.

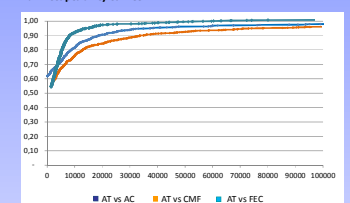
To assess the robustness of our findings, we performed a probabilistic sensitivity analysis by incorporating probability distribution of the input variables by means of a second order Monte Carlo Simulation: each simulation is based on a different value drawn randomly from the distribution of each variable. We used 1,000 second order Monte Carlo simulations. This analysis was based on the distributions of all input variables.

Fig. 2a: Probabilistic Sensitivity Analysis



Source: IPF own calculations

2b: Acceptability curves



Monte Carlo probabilistic sensitivity analyses results of 1,000 trials plotting incremental cost versus incremental effects (Fig. 2a) and based on this to create acceptability curves to assess the likelihood of the comparators being cost-effective over a range of willingness to pay values in the German setting. Sensitivity analysis revealed that AC is cost effective compared to AT in more than 94% of the simulations with a willingness to pay of 30,000 €; CMF in 90% and FEC in 97% of all simulations (Fig. 2b).

Conclusion

Economic analyses have become an integral component in the evaluation of interventions or treatments, including adjuvant chemotherapy for breast cancer whereupon the value-for-money for older well established treatment options is still not fully understood. The analysis demonstrates that AC, CMF and FEC chemotherapy were cost-effective alternative compared to AT. AC and CMF are associated with a clear cost advantage and comparable quality-of-life and life years. FEC leads to a higher quality of life and life years gained. From a health economic perspective, replacing cyclophosphamide by a taxane shows no additional value for money in the setting of adjuvant chemotherapy in breast cancer patients. From a cost-minimization viewpoint AC remains the dominant strategy up to a price of 0.33 €/mg (current price is 0.02 €/mg)."

References

- Goldstein LJ, O'Neill A, Sparano JA, et al.: Concurrent Doxorubicin Plus Docetaxel Is Not More Effective Than Concurrent Doxorubicin Plus Cyclophosphamide in Operable Breast Cancer With 0 to 3 Positive Axillary Nodes: North American Breast Cancer Intergroup Trial E 2197. J Clin Oncol 26 (2008): 4092-4099
- Fisher B, Brown AM, Dignity NV, et al.: Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: Results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 8:1483-1496, 1990
- Moss HB, Donald MD, Berry DA, et al.: Adjuvant Chemotherapy in Older Women with Early-Stage Breast Cancer. NEJM Vol 360, No 20, May 2009
- Roche H, Fumoleau P, Spielmann M, et al.: Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: The FNCLCC PACS 01 trial. J Clin Oncol 24:5664-5671, 2006
- Levine MN, Bramwell V, Pritchard K, et al.: Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer: National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 16:2851-2858, 1998
- Karmon J, Brown J, and the Adjuvant Breast Cancer (ABC) Steering Committee: Tamoxifen plus chemotherapy versus tamoxifen alone as adjuvant therapies for node-positive postmenopausal women with early breast cancer: A stochastic economic evaluation. Pharmacoeconomics 20:119-137, 2002

Additional Literature with the author