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SPECIAL ARTICLE

How to make the best use of limited resources in breast cancer treatment - experiences in Bosnia & Herzegovina

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Summary

Availability of effective treatment has been shown to have a profound, positive impact on survival of breast cancer patients. However, with passing of time treatment of breast cancer has become more complex and associated with increase of costs that puts an enormous burden on health care resources. In order to compare the costs and outcomes of different treatments, we have made our own assessment of costs of breast cancer treatment based on the existing situation in Bosnia & Herzegovina (B&H) and data available from the relevant literature. In B&H costs of breast cancer therapy constitute about one third of the total cost for all tumor types therapies, and this is proportional to the relative number of the treated patients. Prices of overall treatment vary predominantly according to the use of specific adjuvant chemotherapy (CT) and hormonal therapy (HT). FAC (5 fluorouracil/doxorubicin/cyclophosphamide) is 6 times more expensive than CMF (cyclophosphamide/methotrexate/5 fluorouracil), higher doses of epirubicin in $FE_{100}C$ are twice as high compared with FAC. Inclusion of taxanes further increases costs (40-fold for AC [(doxorubicin/cyclophosphamide) + paclitaxel ×4]; 60-fold for TAC with docetaxel; 70-fold for dense-dose regimens in relation to FEC). Treatment with aromatase inhibitors is 11-13 times more expensive compared to tamoxifen. Therapy of metastatic disease is heterogeneous, and it is likely to prolong median survival by 14 months on average. Overall costs vary according to specific treatment modalities used. From CMF and FEC to trastuzumab and docetaxel prices have increased 300 times. All health care systems have a limited budget, but wise use of health care resources is of special importance in countries in transition with evident weakness in economy. In the early breast cancer (EBC) setting, therapy should be individualised according to evidence-based data and respecting available resources. In metastatic disease (MBC) it should be based on risk factors, predictive factors, toxicity, preference of the patient herself and available resources, and weighted against effect on quality of life and treatment costs.

Key words: breast cancer, treatment, treatment costs

Introduction

Carcinoma of the breast is the most common tumour in women. It constitutes 21% of all cancers in females worldwide, and 25-31% in developed countries [1]. The incidence of breast cancer has risen steadily over the past decade, but mortality has been falling since the late 1980s (about 30% in UK, 22% in USA, 25.5% in Denmark). The mortality/incidence ratio is 0.6 worldwide but less than 0.3 in developed countries [2].

The reduction in mortality from breast cancer is partly due to earlier stage at presentation, and partly to changes in therapy [3,4]. Availability of effective treatment is - besides the extent of disease, patient and tumour characteristics - one of the most important prognostic factors in breast cancer.

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Therapy has been shown to have a profound, positive impact on survival in breast cancer patients. However, treatment of breast cancer has become more complex and associated with considerable increase of costs. It puts an enormous burden on patients and health care resources. That, more and more frequently, raises questions and discussions about cost-effectiveness of the different therapeutic manipulations.

The costs consequences of breast cancer treatment varies from country to country, and depend on the stage of cancer when therapy is initiated and the specific treatment option used.

Resources are nowhere unlimited. All health care systems have a limited budget, and no one can provide all the technically feasible, or even all potentially beneficial, treatments.

Still, wise use of health care resources is of special importance for countries in transition, with evident weakness in economy affecting employment levels and insurance coverage. That way such countries must confront questions such as:

- How much is society able and willing to spend on the treatment of cancer; can the costs threaten to overwhelm ability to pay?
- Are co-payments necessary and possible?
- How can we determine whether therapeutic interventions are worth their immense costs?
- How to make the best use of limited resources in cancer treatment?

Oncologists will face those discussions more frequently. As physicians, their primary responsibility is to serve as advocates for patients, and neither want nor are equipped to address difficult questions of social policy. On the other hand, ethical reasoning, that builds a framework for careful thought how and why certain decisions may be made (besides autonomy, do no harm, strive to do good), includes justice as well [5]. Health care professionals must have due regard for the population at large, for example by the fair use of resources.

The purpose of this article was to contribute to a better understanding of breast cancer treatment cost-benefit. In order to compare the costs and outcomes of different treatments, we assessed the costs of breast cancer treatment based on the situation in B&H and data available from the relevant literature. Our aim was not to make a precise economic evaluation and perform cost-effectiveness, cost-utility or cost-benefit analyses since these belong to the field of health economics.

In this article we present very briefly the situation related to breast cancer therapy in our country. In addition, we analyzed separately treatment of EBC confined to the breast and axillary lymph nodes, and treatment of recurrent (RBC) or MBC, as the time of treatment initiation is critical in benefit assessment. We used data from the Register of Malignant Tumours of the Clinical Centre, University of Sarajevo, and the Department for Health Insurance, Federation of B&H.

Situation in Bosnia & Herzegovina

B&H does not have a proper cancer registry for the population nor does it possess precise data of cancer incidence. It was estimated that the incidence of breast cancer in our country is 68.44 per 100,000 women, and 1,373 new cases are registered each year [6]. Still, according to the Register of Malignant Tumours of the Clinical Centre, the incidence rate is rather higher: in the canton of Sarajevo it was 91.6 per 100,000 women in 2004, similar to the one in Croatia and Slovenia [7,8]. This means that 1,700 new cases of breast carcinoma per year could be expected in our country.

Inefficient early detection creates great limitations in terms of breast cancer control in B&H. A large proportion of women with breast cancer still present with advanced disease. With the exception of the canton of Sarajevo, organised screening programs have not been developed and implemented. Mammography is largely limited to regional hospitals.

Surgery is usually readily available in B&H. Although many surgeons are familiar with conservative operations, radical mastectomy outweighs other surgical approaches, most likely due to more advanced disease stages on presentation. Radiotherapy (RT) is performed only in the Clinical Centre, University of Sarajevo, and the equipment can be considered modern. The waiting time for starting adjuvant RT is up to 1 month, for palliation between 2 and 3 weeks. CT and HT of breast cancer is exercised mainly in 4 University Oncology Clinics (Sarajevo, Banja Luka, Tuzla and Mostar).

Starting with the year 2002, financing of RT, CT and HT has been centralised in a part of B&H (Federation of Bosnia and Herzegovina - FB&H), that makes up 51% of the whole territory of B&H with about 2,400,000 inhabitants. The percentage of oncology drugs from the total drug cost in FB&H is 4.3%. Health Insurance has issued a list of 52 anticancer drugs, which contains the indications of each specific compound as well. The main drugs necessary for breast cancer treatment, including aromatase inhibitors, taxanes and trastuzumab in limited amounts, are available. The relative costs of the main anticancer and supportive care agents used in the treatment of breast carcinoma are shown in Table 1.

Table 1. Relative costs of the main anticancer and supportive care drugs used in the treatment of breast cancer

Drug	*Cost (%)*	*Drug*	*Cost (%)*
Docetaxel	27.00	Paclitaxel	5.09
Epirubicin	12.02	Doxorubicin	3.03
Letrozole	11.04	Tamoxifen	2.77
Capecitabine	8.83	Gemcitabine	1.95
Pamidronate	7.45	Filgrastime	1.78
Exemestane	6.37	Cyclophosphamide	1.62
Trastuzumab	5.12	Ondasetron	1.17
		Others	3.64

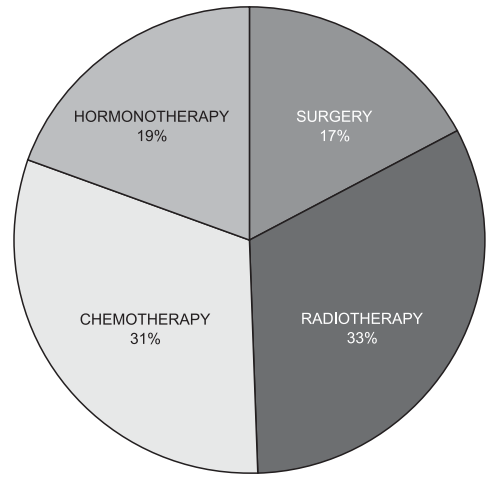


Figure 1. Relative prices of primary breast cancer treatments.

Treatment of breast cancer is complex and associated with the use of different therapeutic modalities and new drugs. It is thought that therapy of breast cancer is more costly than treatment of other tumor types. However, according to our data, costs of breast cancer therapy make up about one third of the cost of treatment for all tumor types, that is proportional to the relative number of the treated patients (in 2003 and 2004 breast cancer made up 27.5% and 29.27% of all treated cancer patients, respectively). Apart of believes, therapy of breast cancer probably does not cost more than treatment of other tumor types.

Treatment of early invasive breast cancer

The goal of therapy of early operable breast cancer is cure that can be achieved in 40-98% of the patients, depending on prognostic factors. Treatment of EBC is comprehensive and requires a multidisciplinary approach. Surgical intervention, RT, HT, CT and supportive drugs are costly. Relative prices of standard breast cancer treatment, which includes total or conservative mastectomy with axillary lymph node dissection, 6 cycles of FEC, RT of the chest wall and/or lymph nodes and 5 years of tamoxifen are presented in Figure 1. Still, this combined therapy is not necessary for all of the patients.

Surgery for EBC has involved modified radical mastectomy, axillary lymph node dissection, or breast-conserving surgery. There is no evidence that more radical surgery than mastectomy is beneficial in EBC. It is clear that modified radical mastectomy and breast preservation with RT are comparable in terms of long-term results [9].

The trials are very consistent regarding the effect of RT on locoregional breast cancer recurrence. Overall, the use of RT is associated with reduction in local recurrence by 66%, and according to some more recent trials by 75% (RT vs. non-RT, 8.8% vs. 27.2%, respectively, at 10 years). Long-term breast cancer mortality appears to be reduced by about 5% in the 5-15 years period. However, there is increase of mortality from other causes by 3-4% in 10 years [10,11]. There is little evidence for deciding which field to irradiate, but locoregional recurrence rates are high when more than 4 axillary nodes are involved or the primary tumour exceeds 5 cm in diameter. Most centres recommend RT in this case. For smaller, node-negative tumours, there is general consensus that RT is unnecessary. Uncertainty remains about the usefulness of RT for smaller tumours with 1-3 positive nodes [9].

RT after breast-conserving surgery reduces significantly breast cancer recurrence rate (RT vs. non-RT, 2.3% vs. 8.8%, respectively). There are no significant differences in the rates of distant metastases, contralateral breast cancer or second primary cancers between irradiated and non-irradiated patients. In women over 55 with small invasive tumours, recurrence rates were 11% and 6% with and without RT, respectively [10,11], meaning that 95% of the patients may receive RT unnecessarily. In other studies advantages of RT in women over 60 are very small, without survival benefit [12].

Adjuvant CT has changed the treatment of EBC and has become widely accepted. A retrospective analysis of clinical trials from the Early Breast Cancer Trialists' Collaborative Group has shown that the use of CT was connected with 14% relative and 4.4% absolute death reduction compared with no CT administration [13]. Adjuvant systemic CT for node-positive EBC produced significant proportional reduction in mortality (27% under 50 years, 11% between 50 and 69 years, respectively) during 10 years. Proportional

reduction in recurrence after 5 years is 35% for women under 50 years and 20% for those over 50 years. Polychemotherapy improves 10-year survival by 7-11% in women aged less than 50 years, and by 2-3% in those older than 50 years. Regimens with an anthracycline were superior to non-anthracycline-containing regimens for recurrence and possibly for 5-year survival (69 vs. 72% 5-year survival) [13-16]. As a result, FAC or FEC have become standard adjuvant treatment for more patients with EBC. The addition of taxanes demonstrated a clear advantage, but taxane-containing regimens are not yet standard therapy for all patients with EBC [17-20].

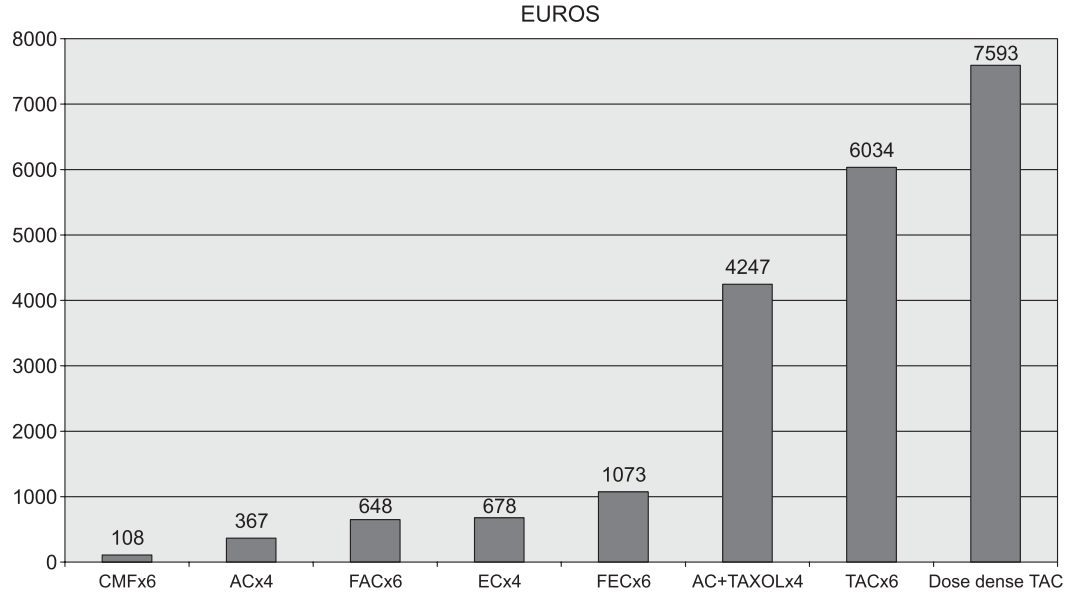
Tamoxifen is one of the earliest systemic therapies used in breast cancer and it quickly became widely used because of its efficiency and good tolerability. Tamoxifen is a gold standard for hormone-dependent breast cancer therapy. 5-year adjuvant tamoxifen clearly improves the 10-year survival and disease-free survival of women with ER-positive tumours or with tumours of unknown ER status (26% proportional reduction in mortality and 47% proportional reduction in recurrence during 10-year period). Absolute 10-year survival improvement is 5.5% (tamoxifen vs. no tamoxifen, 78.9% vs. 73.3%, respectively) [21,22]. In premenopausal women there is now evidence that the combination of ovarian suppression and tamoxifen (goserelin + tamoxifen) is superior to either manipulation alone [23,24]. In postmenopausal women aromatase inhibitors are at least as effective and probably slightly more effective than tamoxifen, with a change of toxicity profile [25-30].

Costs of overall treatment of EBC vary according to the use of specific adjuvant CT and HT agents. Although new drugs theoretically can have a positive, negative or neutral cost impact, the use of new treatment options is almost always translated into higher costs. FAC is 6 times more expensive than CMF, higher dose of epirubicin in $FE_{100}C$ is twice as expensive compared with FAC. Inclusion of taxanes further increases costs (40-fold for AC + paclitaxel ×4; 60-fold for TAC with docetaxel; 70-fold for dense-dose regimens in relation to FEC). Treatment with aromatase inhibitors increases costs 11-13 times compared with tamoxifen (Figures 2, 3).

How can we determine whether different treatment options are worth their costs? Is it possible to save on treatment costs without compromising therapeutic results? As it is very difficult to directly answer these questions, we just tried to present available data on the effectiveness of treatment modalities in EBC therapy. We compared the outcomes of different treatments and a mean of total costs per patient per treatment (Table 2). A mean difference of total costs between different treatments can be easily calculated by subtracting one mean costs from the other, as well as a percent increase in costs.

Treatment of metastatic and recurrent disease

Metastatic and recurrent breast cancer is more heterogeneous than most other cancers. This group includes patients with metastases at diagnosis (MBC), and patients with local or distant recurrent disease



For abbreviations see footnote of Table 2

Figure 2. Prices (Euros) of chemotherapy in primary treatment of breast carcinoma.

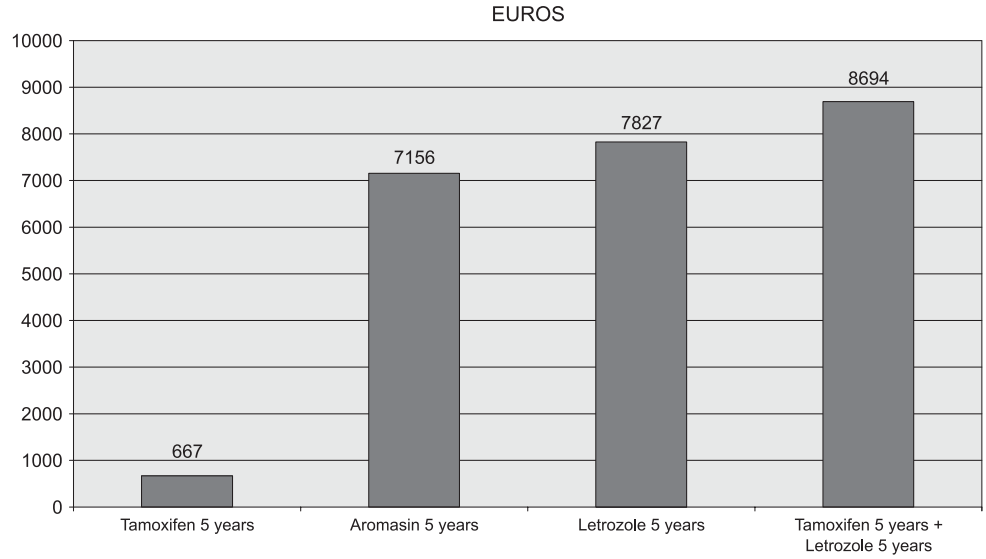


Figure 3. Prices (Euros) of hormonal therapy in primary treatment of breast carcinoma.

(RBC). According to historical data, median survival of non-treated patients with non-operable breast cancer ranges between 30.2 and 39.8 months [31-33].

Active treatments for MBC and RBC include CT, HT, RT and biological therapies (BT). The goal of treatment is to prolong survival, to palliate the symptoms and to preserve the quality of life. Unlike many other cancers, there are no randomised trials of CT, HT or BT vs. best supportive care. But strong indirect support for the effects of anticancer therapy on survival in MBC patients comes from two sources:

1. CT and HT prolong survival in women with EBC.

2. Existing trials of CT, HT and BT in MBC also provide indirect evidence of efficiency (response rate and time to progression).

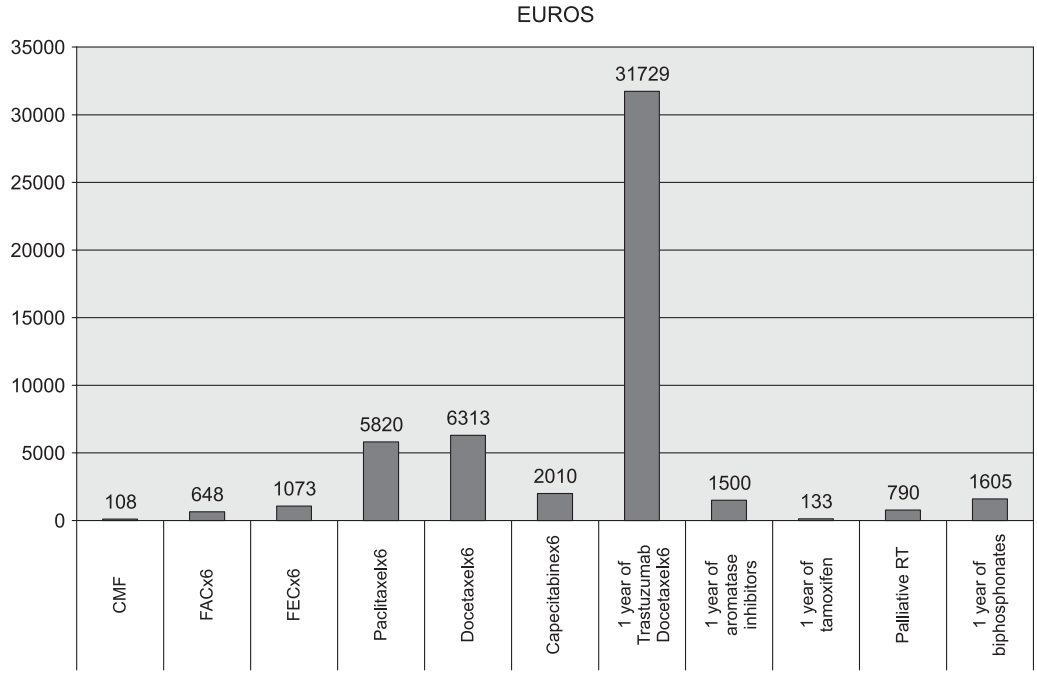
There is overwhelming evidence that both HT and CT prolong survival in MBC. Without CT, the median survival among patients with MBC is about 2.7 years [34,35]. The availability of CT, HT and BT agents further extended the median survival to 4 years. But despite the diversity of options, there is not yet evidence that the new therapies increase cure rates [35,36].

The decision about which particular CT regimens to use will depend on a number of factors. Polychemotherapy is superior to single-agent therapy. Regimens

Table 2. Benefit and prices of treatment modalities in primary therapy of breast cancer

Treatment modality	*Ref.*	*Relative benefit*		*Absolute benefit*		*Price in Euros*
		Recurrence risk reduction (%)	*Death risk reduction (%)*	*Recurrence risk reduction (%)*	*Death risk reduction (%)*	
CMF ×6 vs. no CT	24	24	14	3	4	108 vs. 0
FAC ×6 vs. CMF ×6	24	12	11	4	5	648 vs. 108
AC ×4 vs. CMF ×6	25					367 vs. 108
$FE_{100}C$ ×6 vs. CMF ×6	26	12	11	4	5	1073 vs. 108
AC ×4 + Taxol x4 vs. AC ×4	27	17	18	5	3	364 vs. 4247
TAC vs. FAC	28	28	30	7	6	6034 vs. 648
Dose dense AC+T or A,C,T vs. classical AC+T or A,C,T	29	18	8	7	2	7593 vs. 4247
Tamoxifen 5 years	24	47	25		5.5	667
Tamoxifen 5 years + Letrozole 5 years vs. Tamoxifen 5 years	30		39	5	3.8	8694 vs. 667
Aromasin 5 years vs. Tamoxifen 5 years	31	32	27	4.7		7157 vs. 667
Exemestane 5 years vs. Tamoxifen 5 years	32	17	15	3.6	2.4	6840 vs. 667

C: cyclophosphamide, M: methotrexate, F: 5-fluorouracil, A: doxorubicin, E: epirubicin, T: docetaxel, CT: chemotherapy



For abbreviations see footnote of Table 2

Figure 4. Treatments prices (Euros) of recurrent/metastatic breast cancer.

containing anthracyclines are superior to non-anthracycline regimens [37,38]. If an anthracycline combination is taken as a reference point, then taxane-containing regimens are clearly very effective compared to non-taxane regimens [39-44]. Increasing dose density has not improved survival for anthracycline-containing combinations [45]. CT plus trastuzumab compared to CT alone gives better progression-free survival and a trend to better overall survival. Efficiency is seen only if there is evidence of amplification of HER2 gene [46,47].

There is moderately strong evidence that using HT first (in hormone receptor-positive or unknown disease) is reasonable and not disadvantageous. The combination of HT and CT does not appear to be of benefit over either modality alone [48,49]. It is generally believed that CT may be preferable to HT in the presence of rapidly progressing visceral disease.

RT achieves good pain control and prevents complications of metastatic bone disease.

Bisphosphonates can reduce skeletal complications of bone metastases by 14%. In 4 studies significant improvements in pain were reported. Biphosphonates do not appear to affect survival in women with advanced breast cancer. In 3 studies in women without bone metastases, there was no significant reduction in skeletal related events [50].

Costs of overall therapy of metastatic disease vary according to specific treatment modalities used. The cost estimates presented in Figure 4 are exclusively for drugs and specific supportive medication. They do not include the costs of preparation and hospitalization or costs arising from the treatment of complications and side effects.

Discussion

Treatment of breast cancer is becoming more complex and associated with the use of different therapeutic modalities and new drugs. Its costs relate with the stage of disease, aim of therapy, the specific treatment option used, and vary from country to country.

It is unlikely that overall costs of breast cancer treatment could be reduced. There is currently no way for effective prevention of breast cancer and the number of patients will increase. On the other hand, therapy is becoming more effective, more complex and more expensive.

Health Systems struggling to manage costs should focus on ensuring adequate reimbursement for cancer treatment. Financial planning and continuous monitoring in breast cancer treatment is inevitable and should include priority drug budget, and a new-product budget as well. Economic evaluation requires evidence on the clinical effectiveness of treatment to estimate the outcomes.

In addition to finance experts, cost-effective analyses must include oncology professionals as well.

Among them, there certainly has been no will to deny coverage for effective interventions on the basis of cost. But, cancer therapies are so expensive that they need to be rationalized. In case of limited resources, their use must be "reasonable and necessary". Health care professionals must have due regard for the population at large by the fair use of resources. Treatment of certain patients should be appropriate and in relation to the society as a whole.

In the treatment of breast cancer new drugs regularly emerge, increasing the number of alternative treatments. Even if the evidence suggests the new drug or treatment to be more effective than a previous one, judgement is required as to whether it is cost-effective to provide the new drug or treatment at all. Despite ethical issues associated with putting a monetary value on life, health economics, and economic evaluation in particular, can help illuminate such a decision through a rigorous consideration of the costs and outcomes of alternative treatments.

A new treatment is often more costly but also more effective than a previous one [17-30]. In the case of B&H, as well as in many other countries, there is no numerical value for the threshold value below which a treatment can be considered cost-effective. Therefore, an element of subjectivity is left to decision makers to judge the treatment's cost-effectiveness.

The price of treatment of operable breast cancer varies, mainly due to the specific adjuvant CT used. In EBC setting, therapy is substantially more cost-effective. The primary treatment of EBC should be optimal, as it offers a chance for cure. As this treatment is also complex and differs in price, it is important to carefully select patients for the most appropriate adjuvant therapy. Therapy should be individualised according to evidence-based data and relevant available resources. Not all patients need RT, even after breast-preserving surgery. Not all patients will benefit from most expensive systemic treatment. There is still place for CMF. FEC/FAC and tamoxifen are still gold standards in the treatment of EBC [17-22]. It is important to define which patients will benefit from taxanes and/or aromatase inhibitors in the adjuvant setting [27,28].

Oncologists may face even more difficult situations on how to make the best use of limited resources in the treatment of metastatic/recurrent breast cancer. Overall, treatment of metastatic disease is more expensive, reflecting key drugs (cytotoxics and hormonal agents) and hospitalization costs associated with it. Better systemic therapy has considerably improved prognosis. Although clinical data differ somehow, it is likely that systemic treatment prolongs median survival beyond 30 months [34,35]. While there is evidence of increased response rate with CT, no clear evidence of significant difference in overall survival is documented. Considering quality of life issues is particularly important in the treatment of metastatic/recurrent breast cancer, where many treatments obtain modest improvements in response or survival at the expense of toxicity and dramatically (sometimes) increased costs. A decision about which particular CT regimen to use will depend on a number of factors, based on risk factors, predictive factors, toxicity, preference of the patient herself and available resources, and weighted against the impact on quality of life and treatment costs.

The effectiveness of breast cancer screening is consistent in many ways. Breast cancer screening and early disease detection have resulted in earlier diagnosis, and thus have the potential to increase the proportion of patients who receive treatment while they still have early-stage disease, which, in turn, results in improvement of survival and relative cost benefit. Early detection of breast cancer can be a wise use of health care resources.

References

1. Parkin MD, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999; 49:330-364.
2. Brown P. UK death rates from breast cancer fall by a third. Br Med J 2000; 321: 849.
3. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer death down 25% in year 2000 at ages 20-69 years. Lancet 2000; 355: 1882.
4. Tabar R, Vitak B, Chen HHT, Yen MF, Duffy SW, Smith RA. Beyond randomised control trials; Organised mammography screening substantially reduces breast carcinoma mortality. Cancer 2001; 91: 1724-1731.
5. Beauchamp TL, Childress JF (eds). Principles of biomedical ethics. Oxford University Press, Oxford, 1994.
6. GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide. Version 1.0. IARC Cancer Base No. 5, Lyon, IARC Press, 2001.
7. Register of Malignant Tumours of Clinical Centre, University of Sarajevo. Sarajevo 2002.
8. Obralić N, Gavrankapetanović F, Dizdarević Z et al. Regional comparison of cancer incidence. Radiol Oncol 2004; 38: 145-151.
9. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomised trails . N Engl J Med 1995; 333: 1444-1455.
10. Liljewrgen G, Holmberg L, Bergh J et al. 10-year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: A randomised trial. J Clin Oncol 1999; 17: 2326-2333.
11. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects of long - term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet 2000; 355: 1757-1770.
12. Veronesi U, Luini A, Galimberti V et al. Conservation ap-

proaches for the management of the stages I/II carcinoma of the breast: Milan Cancer Institute Trials. Wld J Surg 1994; 18: 70-75.
13. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998; 352: 930-942.
14. Fisher B, Anderson S, Tan-Chiu E et al. Tamoxifen and Chemotherapy for Axillary Node-Negative, Estrogen Receptor–Negative Breast Cancer: Findings From National Surgical Adjuvant Breast and Bowel Project B-23. J Clin Oncol 2001; 17: 931-942.
15. French Adjuvant Study Group. Benefit of a High-Dose Epirubicin Regimen in Adjuvant Chemotherapy for Node-Positive Breast Cancer Patients With Poor Prognostic Factors: 5-Year Follow-Up Results of the French Adjuvant Study Group 05 Randomized Trial. J Clin Oncol 2001; 16: 602-611.
16. Citron ML, Berry DA, Cirrincione C. Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003; 21: 1431-1439.
17. Henderson IC, Berry D, Demetri G et al. Improved disease free and overall survival from the addition of sequential paclitaxel but not from the escalation of doxorubicin dose level in the adjuvant chemotherapy of patients with node-positive primary breast cancer. Proc Am Soc Clin Oncol 1998; 17: 101a (abstr).
18. Thomas E, Buzdar A, Theriault R at al. Role of paclitaxel in adjuvant therapy of operable breast cancer: preliminary results of a prospective randomised clinical trial. Proc Am Soc Clin Oncol 2000; 19: 74a (abstr).
19. Henderson C, Berry DA, Demetri GD et al. Improved Outcomes From Adding Sequential Paclitaxel but Not From Escalating Doxorubicin Dose in an Adjuvant Chemotherapy Regimen for Patients With Node-Positive Primary Breast Cancer. J Clin Oncol 2003; 21: 976-983.
20. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP. TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up. Proc San Antonio Breast Cancer Meet 2003 (abstr #45).
21. Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomised trials among 28896 women. N Engl J Med 1988; 319: 1681-1692.
22. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overiew of the randomised trials. Lancet 1998; 351: 1451-1467.
23. Jakesz R, Hausmaninger H, Kubistra E et al. Randomised adjuvant trial of tamoxifen and goserelin versus CMF. Evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone responsive breast cancer- Austrian Breast & Colorectal Cancer Study Group Trial 5 . J Clin Oncol 2002; 20: 4621-4627.
24. Klijn JGM, Beex L, Mauriac L et al. Combined treatment with buserelin and tamoxifen versus tamoxifen alone in premenopausal women with early breast cancer: a randomized study. J Natl Cancer Inst 2000; 92: 903-911.
25. Goss PE, Ingle JN, Martino S et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003; 349: 1793-1802.
26. Coombes RC, Hall E, Gibson L et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004; 82 (Suppl): S6 (abstr #1).
27. ATAC Trialists Group. Anastrazole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomized trial. Lancet 2002; 359: 2131-2139.
28. Goss PE, Ingle JN, Martino S et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003; 349: 1793-1802.
29. Coombes RC, Hall E, Gibson LJ et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004; 350: 1081-1092.
30. Howell A, Cuzick J, Baum M, Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005; 365: 60-62.
31. Honig SF. Treatment of metastatic disease. In: Harris JR, Lippman ME, Morrow M et al (eds): Diseases of the Breast. Philadelphia: Lippincott-Raven Publ, 1996, pp 669-734.
32. Falkson G, Holcroft C, Gelman RS et al. Ten-year follow-up study of premenopausal women with metastatic breast cancer; an Eastern Cooperative Oncology Group study. J Clin Oncol 1995; 13: 1453-1458.
33. Yeatman TJ. The natural history of locally advanced primary breast carcinoma and metastatic disease. Surg Oncol Clin N Am 1995; 4: 569-589.
34. Cardoso F, Di LA, Lohrisch C et al. Second and subsequent lines of chemotherapy for metastatic breast cancer: what did we learn in the last two decades? Ann Oncol 2002; 13: 197-207.
35. Norton L. Salvage chemotherapy of breast cancer. Semin Oncol 1994; 21: 19-24.
36. Bull JM, Tormey DC, Li SH et al. A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer 1978; 41: 1649-1657.
37. Cummings FJ, Gelman R, Horton J et al. Comparison of CAF versus CMFP in metastatic breast cancer: analysis of prognostic factors. J Clin Oncol 1985; 3: 932-940.
38. Falkson G, Tormey DC, Carey P et al. Long-term survival of patients treated with combination chemotherapy for metastatic breast cancer. Eur J Cancer 1991; 27: 973-977.
39. Bontenbal M, Braun JJ, Creemers GJ et al. Phase III study comparing AT (adriamycin, docetaxel) to FAC (fluorouracil, adriamycin, cyclophosphamide) as first-line chemotherapy (CT) in patients with metastatic breast cancer (MBC). Eur J Cancer 2003; 1: 5201-5202.
40. Biganzoli L, Cufer T, Bruning P et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10961 multicenter phase III trial. J Clin Oncol 2002; 20: 3114-3121.
41. Mackey J, Paterson A, Dirix L et al. Final results of the phase III randomized trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first line

chemotherapy for patients (pts) with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 2002; 21: 25a (abstr).
42. Nabholtz JM, Falkson C, Campos D et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol 2003; 21: 968-975.
43. Nabholtz JM, Senn HJ, Bezwoda WR, et al. Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. J Clin Oncol 1999; 17: 1413-1424.
44. Paridaens R, Biganzoli L, Bruning P et al. Paclitaxel versus doxorubicin as first-line single-agent chemotherapy for metastatic breast cancer: a European Organization for Research and Treatment of Cancer randomized study with cross-over. J Clin Oncol 2000; 18: 724-733.
45. Ackland SP, Anton A, Breitback GP et al. Dose-intensive epirubicin-based chemotherapy is superior to an intensive intravenous cyclophosphamide, methotrexate, and fluorouracil regimen in metastatic breast cancer: a randomized multinational study. J Clin Oncol 2001; 19: 943-953.
46. Vogel CL, Cobleigh MA, Tripathy D et al. Efficacy and safety of transtuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002; 20: 719-726.
47. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783-792.
48. The Australia / New Zealand Breast Cancer Trials Group. A randomized trial in postmenopausal patients with advanced breast cancer comparing endocrine treatment and cytotoxic therapy given sequentially or in combination. J Clin Oncol 1986; 4: 186-193.
49. Fossati R, Confalonieri C, Torri V et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomised trials involving 31,510 women. J Clin Oncol 1998; 16: 3439-3460.
50. Pavlacis N, Stockler M. Bisphosphonates in breast cancer. Cochrane Database of Systemic Reviews, Issue 1. Oxford: Update Software, 2002.