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FACULTY OF ECONOMICS

ECONOMIC ANALYSIS OF THE TREATMENT OF TUMOUR DISEASES

PhD thesis

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1. BACKGROUND AND OBJECTIVES OF THE WORK

Due to their prevalence and high mortality, malignant diseases represent a significant healthcare problem worldwide. Approximately 33,000 people die of malignant tumours in Hungary annually, and the number of newly discovered cases may be estimated to be 66,000. Based on the results of completed clinical studies, new, innovative compounds with biological mode of action may bring about a significant improvement. The application of these high efficacy products in the everyday routine may have to do with the boom of expenses detectable in the area of oncologic patient care. The author wishes to explore economical aspects of tumour diseases, exemplified by colon cancer, as Hungary is one of those countries with the worst indicators in terms of colon cancer incidence and mortality rate in international comparison.

This thesis is concerned with actual health economy problems via the example of chemotherapy of colonic cancer. Most importantly, the author attempts to determine the cost increase incurred by the application of innovative substances in large numbers of patients.

Using the example of colon cancer, the thesis aims to estimate the contribution of these innovative substances to the prolongation of survival and to determine the costs incurred by these therapies. By opposing achievable clinical and therapeutic benefits and costs in patient care, the author attempts to evaluate financing from the perspective of the society. The thesis also provides an analysis of the financial background of domestic anti-cancer treatment and highlights tendencies in drug costs in oncology.

A secondary objective of the thesis is to create a pharmaco-economical model, which may be a basis for a similar health economy analysis in other therapeutic areas. The author of this thesis has been engaged with health economy of tumour diseases, and

primarily with the problems of financing high efficiency treatment forms. Hypotheses presented in this thesis have been created on the basis of the author's own observations and by a systematic review of the literature.

H1: Hungarian medical practice has begun to incorporate products, which may provide a health benefit in the treatment of colon cancer, in line with the results of clinical studies. The system of financing applied in Hungary follows literature evidences and high efficiency treatments enjoy support by the state health insurance system.

H2: Application of high efficiency treatments in high numbers of patients has significantly increased the costs of care of cancer patients. From the perspective of the financer, the expansion of expenses is mainly seen in the palliative treatment of advanced diseases. With the appearance of new, high efficiency chemotherapeutic protocols a further rise in expenses is expectable, a main component of which being the cost of drugs.

H3: The therapeutic practice in Hungarian oncology patient care is currently under transformation: the proportion of application of the new, high efficiency drugs is increasing, more treatment is being provided using products containing innovative active substances.

H4: The current system of financing of chemotherapy treatments in the domestic active in-patient care does not reflect the exact costs incurred by healthcare providers. HBCS (Homogén betegségcsoportok / Homogeneous Disease Groups Model) protocols, which are the basis for financing, will cover drug costs and other additional costs of the therapies, but the coverage left for the providing of the necessary conditions other than the cost of drugs shows large variations across the protocols. Owing to this, in certain protocols a limited amount is available to cover costs of the

treatments in addition to drug costs, which presents a problem of financing to the healthcare provider.

H5.a: The use of products that have shown a significant clinical benefit in clinical studies may improve life expectancy of patients suffering from colon cancer and survival time increases. An optimal use of the innovative substances may provide significant health benefit and patients may have a longer disease-free period. Using the results of the clinical studies the efficiency may be estimated, accordingly, survival time as well as disease-free period may be determined.

H5.b: The clinical benefit attainable by these novel high efficiency treatments in the palliative care of colon cancer may only be provided against a steep cost increase, compared to therapies accepted as standard earlier.

H6: Tools of pharmaco-economy permit the calculation of cost increase for a unit of survival time unit won. The order of cost effectiveness of the treatment protocols may be determined by calculating the cost effectiveness ratio increase. The results of this may provide basic aspects to evaluations related to financing as the results may help to decide which therapeutic option is the most cost effective.

2. SUMMARY OF THE RESEARCH, METHODOLOGY, RATIONALE

This thesis explores the epidemiological background of metastatic colon cancer by reviewing domestic and international literature. By presenting incidence and mortality rate, the author stresses the social significance of the disease and, in particular, the significance of the unfavourable domestic data in international comparison. In practical matters, the author has consulted experts of the domestic oncology practice.

Besides a revision of the literature of the role of health economy, a separate chapter discusses the efficacy of first line chemotherapeutic treatment of metastatic colon cancer. The author studied results of clinical studies published in the international literature in the past 10 years. The aim of the systematic literature analysis is to determine the efficiency of different chemotherapeutic protocols, primarily on the basis of their effect on survival time. In addition to results of clinical studies, the author analyses therapeutic guidelines as well. Based on a systematic literature review a therapeutic algorithm is defined, which provides the longest survival to patients, based on current evidences.

The first phase of research, in addition to literature analysis, is based on the evaluation of databases of the National Health Fund (NHF) and IMS summarising drug sales. In this part of the research, the author analyses whether the domestic system of financing covers the expenses of treatments appropriately, in the example of colon cancer. During this, drug costs of the evaluated chemotherapeutic treatments are compared to financing protocols of NHF valid for the accounting of active in-patient care. The thesis continues with a discussion of the transformation of oncology therapeutic routine and its effects in the area of drug costs.

In the second phase of the research, the magnitude of increase in survival time and drug costs of the treatments is calculated with the use of a stochastic model,

developed by the author. The main input parameters of this research are median survival time and median disease-free period from evidences of clinical studies, from these the author determines the expected survival time and the average duration of expected disease-free periods for one patient. The stochastic model helps to calculate the average per patient cost of drugs incurred by the evaluated chemotherapy protocols. Using results of the research, the increase in cost effectiveness is also calculated for the treatment options included in the stochastic model. This could be used to support the determination of the additional cost of prolongation of survival and decrease of mortality by the application of the innovative substances, in the case of the evaluated therapies.

3. OUTCOMES OF THE RESEARCH, CORE RESULTS OF THE THESIS

Research included in the thesis present the aspects of health economy of anti-tumour treatments with the example of first line chemotherapy of metastatic colon cancer. In the first phase of the research, the relationship between drug costs of therapeutic protocols and the practice of financing, and the transformation of therapeutic routine is analysed. This provides a background to the boom of expenses detectable in oncology. This is followed by the determination of increase in survival achievable with the most effective treatment forms, with the help of the model. The results of this permit conclusions about the cost effectiveness of the analysed protocols. So far, no studies have been published in Hungary providing an analysis of costs of the chemotherapy of colon cancer and the achievable gain in survival.

Summary of the research results and conclusions:

1. Evidences from the clinical studies on colon cancer show that only a few of the large number of therapeutic schemes, primarily protocols including substances that modify biological responses, have been able to significantly prolong survival. Hypotheses H1 and H2 state that high efficiency compounds providing long survival times have become prevalent in the domestic clinical practice, which have generated a significant cost increase in the palliative care of the disease under study.

The analysis of the system of financing effective in Hungary shows that treatment protocols are in line with literature evidences. Owing to a continuous update, treatments that have been confirmed to be effective in clinical studies receive social health insurance support within the system of financing of active in-patient care.

The research determines the causes of cost increase detectable within the area of oncology. An analysis of drug expenses demonstrates that sales of drugs used in oncology increased continuously between 2000 and 2009. The analysis of the chemotherapy protocols used in colon cancer shows that drug expenses of one

treatment cycle have increased considerably following appearance of the biological substances. Mainly these innovative therapies, providing break-through treatment results in clinical practice, are the cause of the boom of expenses seen in oncology. Bevacizumab and cetuximab have appeared as substances providing excellent treatment results, but their application is associated with high costs. With irinotecan, oxaliplatin and biological response modifiers gaining ground, total drug costs have increased about 30-fold in the past ten years.

2. Based on evidences in specific literature, it can be determined that treatments, earlier considered as standard, have gradually been replaced in the domestic clinical practice in the past ten years. Hypothesis H3 states that domestic patient care practice follows the evidences of clinical studies.

An analysis of the drug sales figures of NHF and IMS shows that domestic therapeutic practice in colon cancer has changed during the past ten years. Besides 5-FU+LV treatment, used almost exclusively earlier, first irinotecan, then capecitabine and oxaliplatin have appeared as results of clinical studies have become public. Later, besides chemical substances, biotechnology molecules have also become common, which are capable of significantly prolonging patient survival according to results of clinical studies. Drug sales figures show that the number of patients receiving biological substances, including bevacizumab and cetuximab, increases every year.

3. Hypothesis H4 of the thesis states that current financing of chemotherapies used in the domestic active in-patient care does not reflect the exact costs incurred by healthcare providers. A cost analysis of the chemotherapy schemes of colon cancer has shown that the ratio of drug cost shows a significant diversity within the HBCS-based financing protocol. In some of the treatments, chemotherapeutic drugs represent only a few percent of the total cost of the protocol. This ratio may be as high as 80% in the case of biological response modifiers. As there are less resources available for other costs of application of the treatments in the first case, the use of protocols of

higher drug cost is available to the healthcare providers under unfavourable monetary conditions. As the research points out, in the case of saturating treatments with oxaliplatin and cetuximab, the HBCS financing model fails to cover even drug costs in entirety. It is also determined that certain treatment schemes (e.g. 5-FU+LV combinations) in the financing system are designed differently from those in clinical studies.

4. In the second part of the research, the author examines the costs and therapeutic efficiency of the treatment of colon cancer with the help of a stochastic model. Drug costs of therapeutic protocols applied in the Hungarian financing system are determined. Based on results of this analysis, it is found that 5-FU+LV treatments used currently apply doses different from those used in clinical studies. One chemotherapy cycle of one patient in Hungary, costs HUF 429,602 in the case of bevacizumab+irinotecan+5-FU+LV therapy, and HUF 586,617 in the case of cetuximab+irinotecan+5-FU+LV therapy. The author determines that the combined use of bevacizumab+oxaliplatin is not financed in Hungary.

5. Current literature confirms the efficacy of biological response modifiers under clinical research conditions. The formulation of hypothesis H5 refers to efficacy attained in real clinical conditions and states that application of biological response modifiers may result in significant clinical benefits.
Efficacy results of the research show that addition of cetuximab or bevacizumab prolongs patient survival from the date of start of the therapy, as compared to regular cytotoxic therapies. Should suitable patients receive bevacizumab supplementation in addition to irinotecan- or oxaliplatin-containig chemotherapy, expected mean survival would be 1.61 or 1.60 years, respectively. Cetuximab and FOLFIRI treatment of K-ras wild type patients, selected with genetic evaluation, would result in an expected survival of 1.70 years.

6. The author determines the average disease-free period, achievable with biological response modifiers, with the use of the stochastic model. The results indicate that addition of bevacizumab to irinotecan- or oxaliplatin-containing chemotherapy would increase the expectable disease-free period to 8.78 and 8.85 months, respectively. In case of K-ras wild type patients selected with genetic analysis, cetuximab and FOLFIRI treatment would provide 9.35 months of average disease-free period.

7. Health economy research has long been analysing causes of the excessive increase in the expenses of healthcare. Hypothesis H5.b forecasts an increase of expenses related to the application of high efficiency therapeutic alternatives in the treatment of colon cancer.
In his work, the author determines the expected costs of bevacizumab- and cetuximab-containing treatment regimens. The average per patient cost of bevacizumab and IFL protocol in combination is HUF 5.04 million, and the combination of bevacizumab and FOLFOX 4 protocol would be HUF 4.39 million. In case of K-ras wild type patients selected with genetic analysis, drug costs of cetuximab and FOLFIRI treatment would amount to HUF 5.81 million.

8. No cost effectiveness data are available in oncology based on the analysis of the domestic financing environment and clinical possibilities. Hypothesis H6 formulates that, by using a suitable method, the therapeutic option with the most favourable cost effectiveness may be determined.
As a main outcome of this research, it is determined that bevacizumab+irinotecan+5-FU+LV is capable of providing one year prolongation of survival with the least increase of expenses. In addition, bevacizumab in this protocol is capable to provide a significant advantage in survival, irrespective of the results of the genetic evaluation. The additional cost of prolonging survival by one year with the addition of bevacizumab is HUF 11.98 million compared to irinotecan and HUF 49.65 million

compared to oxaliplatin treatment, whereas the additional cost is HUF 34.99 million in cases of K-ras wild type, compared to irinotectan.

9. It may be stated that data of efficiency of chemotherapy protocols used in the current treatment practice are not available in Hungary. Thus, the results of the stochastic model built on clinical studies cannot be compared to the efficiency of the applied therapy. Similarly, expected survival of patients actually undergoing treatment cannot be determined in case of colon cancer and the exact efficiency of the therapeutic protocols, characterised by overall survival, remains unknown. Results of the clinical studies are not suitable for the determination of efficiency of therapies used in Hungary because dosing schemes of 5-FU+LV in protocols used in the daily routine and protocols applied in clinical studies are different.

3.1. Novel conclusions of the thesis

No analysis has been available in Hungary comparing the efficiency of different therapeutic options of colon cancer and drug cost increases, therefore the results of this research provide essentially new information for a health economical evaluation of the disease. The stochastic model developed by the author may be regarded as a novel method for analysis, which may also be used for similar cost effectiveness calculations in other therapeutic areas.

Summary of the important results:

1. The stochastic model has confirmed that the efficiency of treatments applying biological response modifiers is more favourable than the efficiency of those including cytostatic compounds only. Using results of median treatment duration and progression-free survival from clinical studies, mean survival and disease-free period

were found longer in the case of bevacizumab and certuximab than in the case of chemotherapeutic substances applied alone.

2. The stochastic model may be used to determine the average per patient drug costs of treatments that have been found optimal in clinical studies. With regard to cost effectiveness, large differences are seen in the case of treatments containing biological response modifiers. Average per patient drug cost is the lowest in case of the bevacizumab+oxaliplatin+5-FU+LV protocol (HUF 4.39 million). The protocol containing cetuximab would cost HUF 5.81 million per patient.

3. Considering cost effectiveness, multiple differences exist in the cases of examined treatments therefore the results of the research permit novel conclusions from a financial aspect. Based on these, it can be concluded that the application of bevacizumab+irinotecan+5-FU+LV is most favourable of the protocols using biological response modifiers, in terms of cost effectiveness. In this case, increase in the cost effectiveness ratio is HUF 11.98 million/year won as compared to treatment applied without bevacizumab, which is almost triple-fold better than in the case of cetuximab (HUF 34.99 million HUF/ year won).

4. The applied pharmaco-economical method is suitable to determine the cost effectiveness of the biological response modifiers. The model developed by the author is capable of determining costs and efficiency of selected treatments in colon cancer. As the applied research method uses evidences of clinical studies, the calculations are repeatable and may be applied for any other area of therapy. The novelty of the developed model lies in the possibility to quickly draw conclusions on cost effectiveness by an arbitrary expansion of the input parameters. With the help of the model, future results of clinical studies may simply be turned to conclusions about financing.

5. In his research, the author determines that none of the protocols of biological response modifiers have been analysed in randomised, phase III clinical studies on large numbers of patients in Hungary. In the reference handbook „Anti-tumour therapies registered and financed from state healthcare resources based on homologous disease groups 959A-L", the dosing scheme of bevacizumab-containing financing protocols is different from those used in clinical studies. The difference lies in the doses of bevacizumab and 5-FU+LV. It can also be determined that protocols currently financed in Hungary have not been evaluated in clinical studies. Saturating and maintenance doses of cetuximab+irinotecan+5-FU+LV treatments are also different from those known from the literature.

4. Conclusions and recommendations

1. One of the reasons for the excessive increase in costs of the treatment of colon cancer is the appearance and expanding market share of new and innovative drugs. From the results of the research, it is concluded that a wide-spread use of cetuximab and bevacizumab would be associated with a significant increase of drug cost. The application of these treatments is associated with a benefit in survival. Supplementary analysis determining the total cost of care of the disease and analysing the cost of sacrificing benefits becomes possible by expanding the model.

2. The health economy model confirms the outcomes of clinical studies in terms of effectiveness. The results corroborate the conclusion that therapeutic use of bevacizumab and cetuximab may improve life expectancy of patients. Determination of the gain in years of survival, however, needs further research. The calculations of the model cannot be compared to the effectiveness of the current therapeutic practice as data from the latter are not available.

3. It is necessary to establish a patient register, capable of following up effects of therapeutic interventions in the long run. This would permit a comparison between results of clinical studies and the effectiveness of treatments used in everyday therapeutic situations. Such patient register would also permit an analysis of the duration of treatment as an efficacy parameter, which could be used as a basis for decisions about financing.

4. As the work points out, certain high efficiency treatments are not yet available to patients. Bevacizumab+FOLFOX 4 and bevacizumab+XELOX protocols are not available among the domestic therapeutic alternatives. Current regulation does not permit the application of these high efficiency treatments. As clinical results of these regimens show a significant survival advantage, it seems justified to make these

treatment options available for Hungarian patients. A wide-spread use of capecitabine seems especially important, as this treatment is suitable to replace the straining process of intravenous 5-FU treatment. It is practical to consider the results of this research in preparation for a financial decision in these protocols, and to estimate the ratio of costs and attainable efficiency.

5. Further research is needed to conduct an exact analysis of cost effectiveness. Data of current therapeutic routine are missing for such research. Efficacy data of domestic treatment forms could be used as references in the determination of survival advantage, and data of actual costs could be used as a basis for the calculation of cost increase. Should the number of treated patient and the number of applied treatments be available, annual treatment cost of patients suffering from colon cancer could be determined. A prerequisite for all this is a patient register where exact therapeutic routine is recorded.

Important aspects of the usability of the results in practice:

1. The results of the research conducted by the author may be used for decisions about financing in the treatment of colon cancer. The model is suitable to calculate effects of the studied healthcare technology on the annual budget. Following the principle of cost effectiveness, the method is suitable to model the effectiveness of an arbitrary therapeutic protocol.

2. The model may be used as an approach in cases where improvement of clinical results is associated with a significant increase in costs. The model is also suitable for similar analysis in other therapeutic areas, where estimation of budgetary effects and therapeutic benefit calls for an extensive evaluation. The model is suitable to be used by the National Institute for Strategic Health Research and the National Health Fund for the analysis of an arbitrary medical intervention.

3. Results and conclusions of this work may be used for the establishment of the therapeutic guidelines of colon cancer. The author determines expected survival and expected duration of treatment in the different therapeutic protocols based on evidences in the professional literature. If results of the cost of treatments are available, aspects of the financing may also be applied for the establishment of the treatment algorithm of a disease.

4. No data indicating the effectiveness of the actual patient care are available for the entire population of patients suffering from tumours. The model presented in this work may be used for the simulation of long-term effects of therapeutic interventions. The method is especially suited for cases where routinely applied therapies and therapeutic regimens used in clinical studies are identical. The model may help to estimate expectable survival in tumour diseases.

5. Due to the ever-increasing costs of healthcare, the importance of health economy and pharmaco-economy becomes more and more apparent. This body of work provides an example for practical application of a cost effectiveness analysis. The results and the methodology of this work are suitable for use in the education of healthcare professionals, and for the education of technological analysis.

5. Publications in the area of the thesis

Publications in professional journals and studies:

1. **Józsa Gábor** (2005): Hogyan változik az onkológiai kezelések költsége? *Gazdaság és Társadalom*, 16. évf. 2005. 2. szám
2. **Józsa Gábor,** Gerencsér Zsolt (2006): Cost minimalisation analysis of capecitabine versus 5-fluorouracil-leucovorin (5-FU+LV), *The European Journal of Health Economics*, Vol.7, Suppl. 1. 2006 July , DOI 10.1007/s10198-006-0369-7, 0184
3. **Józsa Gábor** (2007): Farmakoökonómiai szempontok daganatellenes terápiák alkalmazásában, XXVIII. OTDK, Doktorandusz Konferencia, Miskolc (Kiemelt minősítést elnyert dolgozatok, ME GTK, Miskolc, ISBN:978-963-661774-5)
4. **Józsa Gábor** (2007): A betegek életminőség-vizsgálatának jelentősége a gyógyszerterápiás gyakorlatban, *Egészségfejlesztés*, XLVIII.évf. 2007. 4. szám, 27-31.
5. **Józsa Gábor** (2007): Cost shifting effect in DRG based anti-cancer therapies in Hungary, *Value in Health*, Vol.10, No. 6, Nov-Dec. 2007, A338, PCN50 (ISSN 1098-3015)
6. Gerencsér Zsolt, **Józsa Gábor** (2007): A rituximab költséghatékonysága relabált follikuláris non-Hodgkin lymphoma fenntartó kezelésében, *Hematológia, transzfúziológia*, 40. évf., 4/2007. December, 340-352.
7. **Józsa Gábor** (2008): Cost Effectiveness in Clinical Oncology-General Aspect and Hungarian Practice, *microCAD 2008.*, (ISBN 978-963-661-829-2)
8. **Józsa Gábor** (2008): Cost diversity of DRG based colorectal cancer therapies in Hungary, *Value in Health*, Vol. 11, No. 3, May-June 2008, A59, PCN16 (ISSN 1098-3015)

Other professional activity in connection with the topic of the thesis:

1. Participation in the graduate education of the university (2008, 2009, 2010), university lectures:
- University of Debrecen, Faculty of Pharmacology (students in the 4th grtade):
Foundations of pharmaco-economy

2. Pharmaco-economy research:
- European benchmarking report on lung cancer (2007) (**Karolinska Institutet**)

- EuroVaQ 2007-2010: European Value of a Quality Adjusted Life Year (**Corvinus Egyetem**, Budapest)

Lectures at scientific meetings:

1. **Józsa Gábor** (2007)**:** A daganatellenes gyógyszeres terápiák költségei a Karolinska jelentés alapján, Kórházi Gyógyszerészek XV. Kongresszusa (SZOTE-GYTK/2007-01/00060)
2. **Józsa Gábor** (2007)**:** Farmakoökonómiai szempontok daganatellenes terápiák alkalmazásában, XXVIII. OTDK, Doktorandusz Konferencia, Miskolc
3. **Józsa Gábor** (2008): Cost Effectiveness in Clinical Oncology-General Aspect and Hungarian Practice, microCAD International Scientific Conference, 2008. Miskolc

Participation in conferences:

1. IME – META I. Országos Egészség-gazdaságtani Konferencia, (2007):
Józsa Gábor (2007)**:** A capecitabine költségminimalizációs elemzése–a finanszírozás megváltoztatásának hatása (poszter),
Józsa Gábor (2007): A rituximab kezelés költséghatékonysági modellje sikertelen tumornekrózis faktor alfa gátló kezelés után rheumatiod arhritisben Magyarországon (poszter).
2. Magyar Klinikai Onkológia Társaság IV. Kongresszusa (2006)
3. 9th Congress of International Society of Pharmacoeconomy and Outcomes Research (2006)
4. 6th World Congress of International Health Economic Association (2007)
5. Magyar Onkológusok Társaságának XXVII. Kongresszusa (2007)
6. Kórházi Gyógyszerészek XVI. Kongresszusa (2008)
7. Magyar Klinikai Onkológia Társaság V. Kongresszusa (2008)
8. 11th Congress of International Society of Pharmacoeconomy and Outcomes Research (2008)