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Cost analysis of chemotherapy in advanced non-small cell lung cancer

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Introduction. Financial constrains on health care delivery have forced decision-makers and resource providers in most countries to identify interventions that combine clinical benefit with cost-effectiveness. Lung cancer is the leading cause of cancer deaths in Poland, with about 20.000 new cases diagnosed annually and approx. 19.000 deaths. Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases. The cost of drugs is not the only component of the overall chemotherapy-related expenditures. Pharmacoeconomic analysis allows to evaluate all costs and select the most cost-effective treatment strategy.

Aim of study. To estimate the direct costs of three different chemotherapy regimens for advanced NSCLC: cisplatin plus etoposide (PE), cisplatin plus vinorelbine (PN), and cisplatin plus gemcitabine (PG).

Material and Method. The analysis was conducted on 87 patients treated between 1997 and 1999 in five institutions. The payer's perspective was adapted and only medical costs were included.

Results. The mean "cost per cycle" (all expenditures used during management of single patient) for PE, PN and PG regimens were 2.530 PLN, 3.609 PLN, and 5.104 PLN, respectively. The cost of anticancer drugs was the principal component, generating the highest expenses for PG regimen, whereas the cost of hospitalization was the most important factor in generating expenses for PN and PE regimens.

Conclusions. The analysis revealed the cost of drugs and the in-patient administration of chemotherapy to be the main sources of expenditure during chemotherapy for advanced NSCLC. The economic evaluation is feasible in Polish conditions and may provide essential information for health care providers and payers. It is mandatory to perform a prospective study with the use of cost-effectiveness analysis.

Analiza kosztów chemioterapii zaawansowanego niedrobnokomórkowego raka płuca

Wstęp. Ograniczone zasoby finansowe zmuszają do szukania dowodów naukowych dla określenia skuteczności i opłacalności poszczególnych metod leczenia. Rak płuca jest najczęstszą przyczyną zgonów na nowotwory w Polsce. Liczba nowych zachorowań wynosi około 20000 osób rocznie, a liczba zgonów – prawie 19000. Około 80% wszystkich nowotworów płuca stanowi rak niedrobnokomórkowy (NDRP). Koszt leków nie jest jedyną składową ogólnych wydatków związanych z chemioterapią. Analizy farmakoekonomiczne, oceniając wszystkie koszty, pomagają w wyborze optymalnych metod leczenia w aspekcie medycznym i finansowym.

Cel badania. Celem badania była ocena, z punktu widzenia płatnika, bezpośrednich kosztów chemioterapii w odniesieniu do trzech programów chemioterapii zaawansowanego NDRP: cisplatyny i etopozydu (PE), cisplatyny i winorelbiny (PN) oraz cisplatyny i gemcytabiny (PG).

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Metody. Analizą objęto 87 chorych leczonych w 5 ośrodkach w latach 1997–1999.
Wyniki. Głównym elementem wydatków w programie PG były cytostatyki, podczas gdy w programach PN i PE – koszty hospitalizacji. Średni koszt cyklu (wszystkie wydatki związane z leczeniem u jednego chorego) przy użyciu schematów PE, PN, PG wynosiły odpowiednio 2530, 3609 i 5104 PLN.
Wnioski. Analiza wykazała, że koszt chemioterapii zaawansowanego NDRP jest związany głównie z kosztami leków i prowadzeniem chemioterapii w warunkach szpitalnych. Analiza farmakoekonomiczna jest możliwa do przeprowadzenia i może dostarczyć ważnych informacji zarówno dla świadczeniodawców, jak i płatników. Niezbędne jest przeprowadzenie prospektywnego badania z użyciem analizy koszt-efektywność.

Key words: non-small cell lung cancer, chemotherapy, cost analysis
Słowa kluczowe: niedrobnokomórkowy rak płuca, chemioterapia, analiza kosztów

Introduction

The total expenses for medical care in most countries constitute a considerable portion of the Gross National Product. At present, an easy and unlimited access to all types of treatment is not possible in any health care system in the world. At the same time, there is an over-consumption of medical services by the societies in general. Increasing financial constrains on health care delivery in most countries force the decision-makers to identify interventions that combine clinical benefit and cost-effectiveness. The choice of treatment in oncology is a difficult ethical issue. One of the reasons is a limited access to some therapeutic modalities due to economic constraints. Pharmacoeconomics, with its array of methods, provides a possibility of assessing costs of procedures and their actual benefits.

Lung cancer is the most frequent malignancy in Poland, with more than 20.000 new cases diagnosed each year and approximately 19.000 deaths. Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer patients (nearly 16.000 new cases annually) and its in cidence is constantly increasing [1]. About 75% of all patients with NSCLC in Poland present with either locally advanced or metastatic disease. These patients cannot be managed with radical surgery. Locally advanced patients are treated with either radiotherapy alone or radiotherapy combined with chemotherapy, but the five-year survival rates are only in the range of 3-10%. Palliative radiotherapy, chemotherapy or best supportive care (BSC), are possible therapeutic options for patients with stage IV metastatic disease. Over the years, the role of palliative chemotherapy in stage IV NSCLC was a matter of discussion. In the last decade growing evidence has supported the value of this method. The recent Cambridge metaanalysis of all randomized clinical trials has shown that cisplatin-based chemotherapy could increase one-year survival by 10% [2]. It was also shown that chemotherapy can relieve cancer-related symptoms in at least 50% of patients [3]. The American Society of Clinical Oncology (ASCO) has issued clinical guidelines for the treatment of unresectable NSCLC [4]. The ASCO guidelines indicate systemic chemotherapy as a standard approach for advanced NSCLC. However, patients should meet certain clinical criteria (e.g. good performance status, stable body weight and assessable disease).

The progress in the treatment of advanced NSCLC depends on the implementation of new drugs with higher activity. Several new agents (vinorelbine, gemcitabine, paclitaxel and docetaxel) have been demonstrated to be more effective and usually better tolerated than their older counterparts. Of particular value is the use of new agents in multi-drug regimens [5-7]. Unfortunately, these agents are considerably more expensive than older drugs [8]. Despite many clinical studies no chemotherapy regimen has been found to be superior to the others. The recent ECOG study of the four most commonly used chemotherapy regimens, including new agents in combination with platinum compounds, has showed similar activity [9]. Many studies have attempted to evaluate real costs of chemotherapy of advanced NSCLC. However, these studies were performed under different economic circumstances and do not necessarily correspond to clinical practice and financial realities in Poland.

The aim of the present study was to estimate the direct costs of three commonly used chemotherapy regimens for advanced NSCLC: cisplatin and etoposide (PE), cisplatin and vinorelbine (PN), and cisplatin and gemcitabine (PG) under Polish circumstances.

Methods

The analysis was conducted on patients treated between 1997 and 1999 in five Polish institutions. We analysed the cases of patients who had received chemotherapy beyond the scope of clinical trials (routine practice). Patients diagnosed with advanced NSCLC who had received at least two cycles of chemotherapy were eligible for analysis. Chemotherapy was administered either in the in-patient or out-patient setting, depending on the institutional preferences and available facilities. Patients who had received preoperative chemotherapy and/or radical radiotherapy were not analyzed. Eighty-seven patients with advanced (stage IIIB not amenable for radical radiotherapy or stage IV) NSCLC were included in the study. Of those, 35 patients received cisplatin (DDP) and vinorelbine (VRB) – PN regimen, 24 patients DDP and gemcitabine (GCB) – PG regimen and 28 patients DDP and etopside (VP16) – PE regimen. The details of the regimens were: PN – DDP 80 mg/m2 on day 1 + VRB 25 mg/m^2 on days 1 and 8; PE – DDP 30 mg/m^2 on day 1, 2 and 3 + VP16 120 mg/m2 on days 1, 2 and 3; PG – DDP 80 mg/m^2 on day 2 + GCB 1000 mg/m^2 on days 1 and 8. All regimens were administered every 21 days; all agents given intravenously. The mean number of administered cycles was 2.6 for PN, 5.2 for PG and 3.8 for PE (Table I). The differences in the mean number of cycles reflected the duration of treatment. Patients receiving gemcitabine-containing chemotherapy achieved better disease

control. Therefore, the duration of chemotherapy (in consequence, the number of cycles) was prolonged compared with other regimens. The differences were considered in the final resources consumption analysis. All groups of patients were similar with respect to age, gender and disease stage (Table I). All pretreatment routine diagnostic procedures were identical in each group of patients. Both laboratory and radiographic examinations were performed according to the same schedule. The costs of certain additional tests (individually required) were included into the analysis. However, they were performed incidentally with no impact on the results. In the analysis, the payee's perspective was adopted and only medical costs were taken into consideration. The medical costs calculated in the study represent real expenditures on the management of patients (hospital-spent days, out-patient visits, all diagnostic procedures, total medication including anticancer and supportive therapy). The above costs were calculated as follows:

- cost of hospitalization (all costs of hospitalization, including the cost of medical personnel),
- cost of ambulatory care (including physical examination; diagnostic tests considered as consumption only if directly related to clinical evaluation of chemotherapy e.g. biochemistry and radiographic tests),
- cost of cytotoxic agents (cost of medication unit available on the market – for VP16 the cost of Vepesid™ was calculated), cost of antiemetic drugs.

The total cost of treatment was calculated by multiplying the mean cost of one cycle by the mean number of cycles. The following costs were not included in the final assessment:

- costs of drug preparation by nurse or pharmacist,
- costs related to dose reductions or omissions,
- costs of therapy necessary to treat side effects of chemotherapy (e.g. neutropoenia, neurotoxicity, etc),
- costs of analgetic drugs.

Total consumption of resources was calculated by multiplying the number of units by price of the unit. The prices of biochemistry and radiographic tests were obtained from the respective laboratory departments, whereas the costs of medication – from hospital pharmacies. Information on costs of hospitalization and ambulatory care, as well as on the consumption of resources, was obtained from the respective hospital financial departments. All costs were calculated in Polish currency (PLN) using prices for the first 6 months of the year 2000. The costs were evaluated for each hospital and every medical intervention separately. The total cost for each patient was divided by the total number of chemotherapy cycles to obtain a mean "cost per cycle". The total costs for the group of patients were divided by the number of patients to obtain a mean "cost per patient".

Results

Assessment of effectiveness

One-year survival rates for patients in respective groups were as follows: PE – 32% (95% CI 19-45%), PN – 37% (95% CI 24-40%) and PG – 42% (95% CI 25-59%). No statistically significant difference was detected among the three groups of patients.

Consumption of resources

The mean "cost per cycle" (all expenditures used during management of single patient) for PE, PN and PG regimens were 2.530 PLN, 3.609 PLN, and 5.104 PLN, respectively. Calculated mean "cost per patient" (average expenditures for the management within each analyzed group) was 9.658 PLN for PE, 9.417 PLN for PN and 26.449 PLN for PG. The detailed calculation of all costs is presented in table II. The cost of drugs was the principal parameter that generated highest expenditures in PG-treated group, whereas the cost of hospitalization was the most important factor generating expenses for PN and PE regimens. Additionally, we performed an analysis of the direct costs in particular institutions. To make these comparisons more relevant we have analyzed the costs in the different institutions for the same chemotherapy regimens. For example, in two institutions using the PE regimen the total direct costs of treatment per patient were 5.509 PLN and 12.275 PLN, respectively. The same

Table I. Clinical characteristics

Regimen / Data	cisplatin-etoposide	cisplatin-vinorelbine	cisplatin-gemcitabine
Number of patients (males/females)	28 (25/3)	35 (32/3)	24 (20/4)
Median age (range)	59.5 (39-73)	58.4 (43-72)	59.4 (44-74)
Stage IIIB/IV	17/11	20/15	14/10
Mean number of cycles (range)	3.8 (2 – 6)	2.6 (2 – 6)	5.2 (2 – 7)
One-year survival ±95%CI (%)	32% (19-45%)	37% (24-40%)	42% (25-59%)

Table II. Mean cost of treatment (PLN per one patient)

	cisplatin-etoposide	cisplatin -vinorelbine	cisplatin-gemcitabine
Cost of cisplatin	312.72	232.12	438.64
Cost of other cytostatics	634.55	3374.04	18477.44
Cost of supportive medications	844.16	313.73	446.40
Cost of hospitalization + ambulatory care and diagnostic procedures	7867.35	6204.40	4911.46
Cost of one cycle	2530.96	3609.08	5104.51
Total cost of treatment	9658.77	9417.61	26449.75

Table III. Total direct cost of treatment per patient according to centre (in PLN)

	PN		PG		PE	
	Centre 1	Centre 2	Centre 1	Centre 3	Centre 2	Centre 4
Cytostatics	5770.4	3145.9	18491.0	19981.8	848.44	1032.92
Supportive drugs	214.4	335.7	709.2	262.3	693.92	974.37
Hospitalization	3162.0	4815.0	844.0	624.4	2146.15	9020.46
Ambulatory costs	642.3	550.8	652.8	184.9	835.69	0.00
Diagnostics	845.0	868.1	1526.4	1375.2	985.17	1246.77

figures for PN were 10.634 PLN and 9.715 PLN (table III).

Discussion and conclusions

It is estimated that diagnosis and treatment of NSCLC accounts for 20% of the total expenditure for the management of all malignancies and approximately 2% of the global health care costs [10, 11]. The results of treatment of NSCLC are still far from satisfactory. Five-year survival from the date of diagnosis is likely in only 12-16% of all NSCLC patients [12]. The unsatisfactory results evoke discussion on the optimal therapeutic strategy for NSCLC, especially on the role of chemotherapy in advanced stages. Chemotherapy, despite its palliative character, has been found to provide modest survival benefit and better quality of life in selected patients with advanced NSCLC.

Cost of drugs is not the only component of the overall chemotherapy-related expenditure. Pharmacoeconomic analysis enables the evaluation of all costs and may facilitate the selection of most optimal treatment based on medical and economic grounds. It compares costs of treatment and clinical results of different therapeutic modalities. An optimal method of pharmacoeconomic assessment is the cost-effectiveness analysis (CEA). With the use of CEA it is possible to make a comparison of financial aspects for standard and newly introduced modalities in the context of their clinical value. CEA evaluates health outcomes and costs of medical interventions. Its purpose is to show the relative value of alternative intervention for health improvement. It can also help decision-makers to weight alternatives and decide which ones meet best their expectations. The results of CEA are usually expressed as a cost-effectiveness ratio (CER) which demonstrates the cost of achieving one unit of health benefit in different groups of patients treated with the use of various interventions. Examples of clinical benefit used in such analyses include the increased response rate, prolonged survival, reduced use of supportive therapy (i.e. antiemetics, analgesics) and palliative radiotherapy, and shortening the duration of hospital stay. These parameters are crucial for the economy of treatment. They are also essential for the optimal management of patients. For example, shorter hospitalization (chemotherapy in an outpatient setting) is associated with both, lower costs and better quality of life of patients [13]. Unfortunately, for the methodological reasons we were not able to perform CEA analysis due to retrospective character of our study.

Several pharmacoeconomic studies have been performed with the aim to select the most cost-effective chemotherapy regimens in advanced NSCLC [14-21]. The results have shown that palliative chemotherapy may be cost-effective. However, those results cannot be generalized, due to large differences in health-care costs and country-specific variations in financing systems. Thus, there is an urgent need to perform separate analysis taking into account the local situation in Poland. Obviously, not all patients with advanced NSCLC are candidates for systemic therapy. It is recommended for patients with good performance status, with no serious comorbidity, with acceptable laboratory parameters (haematology profile, liver and renal function tests) and, preferably, with measurable or at least evaluable disease. For patients who meet the above criteria chemotherapy is justified as a standard care, whereas BSC should be reserved for all other patients. Since the criteria are restrictive, the majority of patients with advanced disease should be offered BSC only. However, due to the increasing number of advanced NSCLC patients in Poland (approximately 8.000 cases newly diagnosed each year), even the thoroughly selected candidates for chemotherapy create both medical and economical challenge.

To the best of our knowledge the present study is the first published analysis of direct costs related to chemotherapy in advanced NSCLC in Poland. Patients in this study were treated in different institutions and chemotherapy was administrated according to standard criteria [22]. The numbers of patients analyzed per each participating institution were low, when compared with the total numbers expected. There were several reasons for the discrepancy. First, only patients receiving chemotherapy beyond the scope of clinical trials were included. Each institution was involved in numerous clinical trials between 1997 and 1999. Second, the study methodology reduced the enrolment of patients – only patients identically diagnosed, staged and monitored were considered. Third, for a significant number of patients we were unable to obtain complete data on the resources consumption retrospectively. Fourth, patients were supposed to receive at least 2 chemotherapy cycles and continue in case of objective clinical benefit. Keeping in mind the rate of objective responses in a range of 20-30% in advanced NSCLC it is obvious that the number of patients analyzed was lower than could be expected from a total number of patients treated. The present analysis was performed retrospectively and was focused on the economical issues of the routine practice. We decided to select chemotherapy

regimens which were most commonly used in Poland during the analyzed period. What is important, we did not intend to identify the optimal regimen. Our aim was to perform a preliminary study in order to verify the feasibility of direct cost estimation in Polish conditions. Three DDP-based chemotherapy regimens were investigated: VP16-containing (PE), VRB-containing (PN) and GCB--containing (PG). In our series all regimens were comparable in terms of clinical efficacy.

The major limitation of this study is its retrospective character. Furthermore, this series included only patients who had received at least two chemotherapy cycles. Since chemotherapy in advanced NSLCL is usually continued until progression (but not exceeding six cycles), in our series patients were "positively" selected by excluding subjects with early progression. The mean number of cycles with PE, PN and PG regimens were 3.8, 2.6, and 5.2, respectively, and this factor contributed considerably to the total costs of treatment. Some recent studies have suggested that in advanced NSCLC there is no benefit in terms of survival, in continuing chemotherapy for more than three cycles in patients with objective response [23]. Therefore it is likely that similar results might have been obtained with the equal number of cycles for each of the three regimens. Importantly, the indirect costs, such as loss of salary and employment absence, have not been taken into consideration. We noted substantial differences in the total cost of treatment between participating institutions. Chemotherapy was administered either in the day-care system or in the hospital. This had major influence on the total expenditure. The differences of accommodation expenditure were minute in relation to the total costs.

Our results definitely require confirmation in a prospective study. Thus, our data must be considered as preliminary. Despite its limitations, the present study provides valuable information on the direct costs of chemotherapy in advanced NSCLC. Moreover, it illustrates the ways of cost saving, i.e. ambulatory administration of chemotherapy, meticulous use of concomitant medication, etc. As mentioned above, this study provides only preliminary estimation of the financial issues related to the treatment of advanced NSCLC. The complete cost-effectiveness evaluation could only be accomplished in a prospective randomized study, which is planned in the nearest future.

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