

1-1-2016

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BALÇIK, PINAR YALÇIN and ŞAHİN, BAYRAM (2016) "Cost-effectiveness analysis of pemetrexed and gemcitabine treatment for advanced nonsmall cell lung cancer in Turkey," *Turkish Journal of Medical Sciences*: Vol. 46: No. 1, Article 25. <https://doi.org/10.3906/sag-1408-4>
Available at: <https://journals.tubitak.gov.tr/medical/vol46/iss1/25>

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Cost-effectiveness analysis of pemetrexed and gemcitabine treatment for advanced nonsmall cell lung cancer in Turkey

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Received: 01.08.2014 • Accepted/Published Online: 08.05.2015 • Final Version: 05.01.2016

Background/aim: The purpose of the study is to determine the cost-effectiveness of the chemotherapy medications that contain gemcitabine and pemetrexed, which are used in the treatment of advanced nonsmall cell lung cancer (NSCLC).

Materials and methods: The study evaluated the effectiveness and cost of platinum-based pemetrexed and gemcitabine treatments as the first-line treatment of advanced NSCLC with the use of the Markov model, and from the perspective of the Social Security Institution. NSCLC costs calculated on the basis of experts' opinions and the effectiveness values calculated by administering the EQ-5D questionnaire to the patients were analyzed. All direct medical costs were included in the model.

Results: While the life-long cost of gemcitabine/cisplatin treatment was determined to be 10,347.45 Turkish lira per patient, it was determined as 17,783.34 for pemetrexed/cisplatin treatment. The incremental cost of pemetrexed/cisplatin treatment is 220,754 per quality-adjusted life year.

Conclusion: Although there is no official threshold value in Turkey, due to the fact that the incremental cost effectiveness ratio exceeds the threshold value calculated on the basis of GDP per capita, it is understood that pemetrexed/cisplatin is not cost-effective in the first-line treatment of advanced NSCLC.

Key words: Cost-effectiveness, pharmacoeconomy, lung cancer, pemetrexed, gemcitabine

1. Introduction

Developed countries expend 3%–6% of their GNP for cancer treatment. Budgetary pressures caused by limited finances and increased costs have directed the attention of service providers and payers to survival and cost-effect assessment of new cancer medication. Policy makers, regulative authorities, and doctors require more extensive information on treatment costs and cost-effectiveness. Economic evaluation presents a comparison opportunity of treatment alternatives in terms of cost and effectiveness. New cancer drugs, which have high added cost per patient and low expected benefit for large patient groups, are very suitable for economic evaluation (1).

Lung cancer has been the most common cancer in the world for many years and has accounted for 12.7% of all newly diagnosed cancers since 2008. According to the 2008 Turkish data of the International Cancer Research Organization, lung cancer in males rated first among cancer diseases with 14,667 cases in 2008. Male lung cancer mortality ranks first with 13,462 cases and represents 31.5% of deaths due to cancer. In Turkey, female

lung cancer incidence ranks fourth among most frequently seen cancer types with 4.5%. Among female deaths due to cancer, lung cancer is listed fourth at 4.8%. According to GLOBOCAN data on all the groups, lung cancer in Turkey is the most frequently seen type at 17.3% and it represents the most deaths at 23.9% (2).

Lung cancer incurs serious costs in terms of diagnosis and treatment. The increasing number of patients causes economic overburden for this type of cancer. When expenditures for all types of cancer treatment are taken into consideration, it is thought that 20% of costs are due to lung cancer. Unfortunately, lung cancer treatment expenditures are very limited when the benefits accrued are considered (3).

Pemetrexed/cisplatin is recommended as a first-stage alternative treatment for advanced nonsmall cell lung cancer (NSCLC), especially in cases of tumor histology with adenocarcinoma or large-celled carcinoma. However, pemetrexed/cisplatin is not yet included in the refund list for the first stage of advanced NSCLC in Turkey.

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The objective of this study is to identify the cost-effectiveness of chemotherapy medication containing the active ingredients of platin-based pemetrexed and gemcitabine used in the first stage of NSCLC treatment.

2. Materials and methods

In this study, a comparative cost-utility analysis was performed for determining the cost-effectiveness of pemetrexed/cisplatin and gemcitabine/cisplatin treatments used in the first stage of advanced NSCLC. Their budget impact in terms of refund decisions was also examined.

Initially, a data collection tool based on the literature was developed for the cost calculation of pemetrexed/cisplatin and gemcitabine/cisplatin treatments used in advanced-stage NSCLC. For the model's cost entries to reflect clinical practice in Turkey, advanced-stage NSCLC treatment-related interviews were held with a specialist panel consisting of medical oncologists. For specialist opinions, interviews were held with 8 medical oncology specialists from 6 reference hospitals; specialists from different hospitals were preferred to encompass different clinical applications.

Based on specialist opinions, the amounts of health resources (medication, examination, radiology, etc.) and percentages used by nonprogression and progression advanced-stage NSCLC patients receiving pemetrexed/cisplatin and gemcitabine/cisplatin were calculated. Calculated use amounts and percentages were multiplied by unit prices to estimate costs for advanced NSCLC pemetrexed/cisplatin and gemcitabine/cisplatin treatment of nonprogression and progression status cases.

The health resources unit prices used in the model were obtained from the Medication Price List of the Ministry of Health and from the Health Application Directive of the Social Security Institution. Drug prices obtained from the Medication Price List were included in the model with retail prices. Health Application Directive Annex 8 was used for examinations, radiotherapy, polyclinic applications, and hospitalization.

Medication costs were calculated according to dosages and use periods, as indicated by specialists. Chemotherapy medication dosage calculation was based on 1.7 m² body surface area. Initially, if the active ingredient had been indicated as medication, then all drugs listed under that ingredient were tabulated by name, mg/µg, tablet count, and price. For each medication container, the tablet count was multiplied by mg/µg per tablet to find the total mg value. The retail sales price of the medication was divided by total mg/µg to calculate the 1 mg/µg price. The average mg/µg price was calculated for all drugs listed under the active ingredient. The calculated average cost for mg/µg was multiplied by the advised dosage, use duration, and percentage of users to find the total cost of the subject

medication. The second route utilized in drug costs calculation was based on the medication brand title used by specialists, instead of active ingredient name.

Effectiveness data used in the model were based on the life quality health measurement of patients. The EQ-5D survey, an international generic tool also referred to as EuroQoL, was used to measure the health-related life quality of patients (4). Individual respondents were expected to define their health status in terms of mobility, personal care, ordinary activities, pain/ailment, and anxiety/depression.

Since patient health status coefficients were not developed in Turkey, after the application of the EQ-5D to advanced stage NSCLC patients, coefficients from the Netherlands and then coefficients from Britain for sensitivity analysis were used to calculate the life quality averages of progression and nonprogression patients in both treatment groups. The life quality coefficients obtained were multiplied by life years in each cycle of the Markov model, and quality-adjusted life year (QALY) for each cycle was determined. After applying reduction to the quality-adjusted years with the exception of first year, the gained QALY was identified.

Pursuant to cost and effectiveness work, the Markov model was formulated to calculate the cost-effectiveness ratio. The Markov model shows the life-long health status transitions of 1000 hypothetical patients. In order to execute the Markov model, transition probabilities were obtained from the literature. According to these utilized probabilities, the Markov model showed that the advanced stage NSCLC patients experienced a life extension of up to 72 months. The total cost for each month of life was calculated. As in gained life-duration calculations, a 3% reduction was applied to the 5 years, excluding the first year, in order to find the life-long total costs per person receiving the pemetrexed/cisplatin and gemcitabine/cisplatin treatments. Then the incremental cost effectiveness ratio (ICER) was calculated and compared to the threshold value to determine whether the treatment was within acceptable limits. In addition, sensitivity analysis was performed to assess the impact of certain critical variables on the result. Finally, the budget impact of both treatment alternatives was examined.

Cost effectiveness analysis in this study was done from the perspective of the Social Security Institution. Model results are presented as incremental cost per incremental QALY gained in life duration.

The Markov model was developed to simulate the transitions typically seen in the clinical practice involving patients receiving advanced stage NSCLC treatment. The phases of the Markov model were defined as nonprogression, progression, and death, where each patient can be in only one of these clinical states at any given time.

3. Results

3.1. Results related to treatment effectiveness

QALY is used as an indicator of treatment effectiveness in the Markov model. The EQ-5D scale was applied via phone to advanced stage NSCLC patients receiving gemcitabine/cisplatin and pemetrexed/cisplatin treatment at the Hacettepe University Oncology Hospital of Ankara University, Cebeci Hospital of Ankara University, İbni Sina Hospital, and GATA Hospital. The EQ-5D survey subjects were 66 patients contacted between 31 December 2012 and 1 March 2013.

The participant patients' basic information is given in Table 1. As indicated in the table, 23 pemetrexed/cisplatin and 43 gemcitabine/cisplatin treatment patients were consulted. Due to the low number of pemetrexed/cisplatin treatment patients in the hospitals, the survey did not have access to more than 23 contributors. While 45.5% of total participants were in nonprogression status, 54.5% were in progression status. Of the 66 survey participants, 28.8% were female and 71.2% were male. When the social status of participants was examined, 19.7% were employed, 18.2% were homemakers, and 62.1% were retirees. Mean age of survey participants was 59.9 ± 8.6 .

The responses of the patients were converted according to the weight used in the Netherlands, since no life quality mean weight is available for Turkey. Thus, health-related

Table 1. Characteristic distribution of study participant patients.

	Frequency	Percentage
Treatment alternative		
Pemetrexed/cisplatin	23	34.8
Gemcitabine/cisplatin	43	65.2
Progression status		
Nonprogression	30	45.5
Progression	36	54.5
Sex		
Male	47	71.2
Female	19	28.8
Working status		
Employed	13	19.7
Homemaker	12	18.2
Retired	41	62.1
	Mean	Standard deviation
Age	59.9	8.6

quality of life (HRQoL) for pemetrexed/cisplatin treatment was found as 0.815 for nonprogression status and 0.638 for progression status. In the case of gemcitabine/cisplatin treatment, the HRQoL value was calculated as 0.707 for nonprogression and 0.631 for progression.

3.2. Results related to costs

Advanced stage NSCLC pemetrexed/cisplatin and gemcitabine/cisplatin treatment costs are shown in Table 2. Advanced stage NSCLC pemetrexed/cisplatin first phase treatment cost of nonprogression status totals 22,098.91 Turkish lira (TL; 1 USD = 2.94 TL as of September 2015). Similarly, the cost of progression status is 21,887.52 TL. In pemetrexed/cisplatin nonprogression status treatment, 69.86% of the total cost is due to chemotherapy, 8.70% adjunct medication used jointly with chemotherapy, and 7.93% examinations performed during the treatment period. When pemetrexed/cisplatin treatment of progression status total cost is examined, the highest expenditure is incurred by chemotherapy medication, followed by drugs accompanying chemotherapy, with the cost of treatment period examinations ranking third.

It is seen that in advanced stage NSCLC gemcitabine/cisplatin treatment, the total cost of the first phase of nonprogression status is 12,822.13 TL, whereas total progression cost is 12,754.47 TL. In gemcitabine/cisplatin nonprogression treatment, 38.70% of the total cost is related to chemotherapy medication, 21.47% to adjunct drugs used jointly with chemotherapy, and 12.38% to examination costs during the treatment. When the progression status is considered in gemcitabine/cisplatin treatment, chemotherapy drug cost ranks first, and adjunct medication and examinations are second and third, respectively.

As exhibited in Table 2, the largest difference between the two treatments is caused by the cost of chemotherapy drugs. For 6 sessions per alternative, pemetrexed/cisplatin treatment costs 15,439.37 TL and gemcitabine/cisplatin treatment costs 4962.60 TL.

3.3. Cost-effectiveness analysis results

Table 3 shows the cost-effectiveness analysis results after reduction is applied. While the life-long gemcitabine/cisplatin treatment cost per patient is 10,347.45 TL, the pemetrexed/cisplatin treatment cost is 17,783.34 TL. The gained-life years at the end of both treatments were found to be 0.810. This equality in both treatments is due to the use of identical transitional probabilities in the Markov model. The QALY values were found by multiplication of gained years of both treatments by life quality scores. Accordingly, although the gemcitabine/cisplatin treatment QALY value was 0.532, in pemetrexed/cisplatin treatment it was identified as 0.566. Hence, although the pemetrexed/cisplatin treatment during the advanced stage NSCLC first phase did not provide the patients with added life

Table 2. Advanced-stage NSCLC treatment cost.

Cost items	Pemetrexed/cisplatin				Gemcitabine/cisplatin			
	Nonprogression		Progression		Nonprogression		Progression	
	Cost (TL)	Percent	Cost (TL)	Percent	Cost (TL)	Percent	Cost (TL)	Percent
Chemotherapy drugs	15,439.37	69.86	15,439.37	70.54	4962.60	38.70	4962.60	38.91
Drugs accompanying chemotherapy	1923.54	8.70	2133.00	9.75	2752.47	21.47	2874.61	22.54
Radiotherapy	885.00	4.00	462.95	2.12	885.00	6.90	462.95	3.63
Consultation	10.20	0.05	25.80	0.12	15.60	0.12	31.20	0.24
Examination costs during treatment	1753.52	7.93	1729.27	7.90	1587.07	12.38	1725.84	13.53
Examination costs during the monitoring period	799.00	3.62	647.86	2.96	898.69	7.01	882.18	6.92
Medication costs during the monitoring period	182.79	0.83	197.54	0.90	619.87	4.83	673.77	5.28
Side effects	882.29	3.99	709.51	3.24	810.43	6.32	561.93	4.41
Polyclinic applications, hospitalization, reports, and chemotherapy administration	223.20	1.01	542.20	2.48	290.40	2.26	579.40	4.54
Total	22,098.91	100	21,887.52	100	12,822.13	100	12,754.47	100

Table 3. Results of cost-effectiveness analysis.

Treatment alternative	Total cost (TL)	Life years	Effectiveness (QALY)	Incremental cost (TL)	Incremental effectiveness (QALY)	Incremental cost effectiveness ratio (ICER) (TL/QALY)
Gemcitabine/cisplatin	10,347.45	0.810	0.32			
Pemetrexed/cisplatin	17,783.34	0.810	0.566	7436.89	0.0337	220,754

compared to the gemcitabine/cisplatin treatment, the former contributed 0.0337 added QALY and yielded an added cost of 220,754 TL per extra gained QALY.

When health technology is considered for approval or refusal, the interpretation of ICER results alone is not sufficient. For a true assessment of results, a threshold of either cost-effectiveness or willingness to pay is required. It is advised that in decision-making processes, ICER should be compared with the threshold value. If the ICER is below or equal to the threshold value, then the cost is deemed effective.

The World Health Organization (WHO) suggests the use of GNP per person ratio as an indicator of the threshold value. According to the WHO, if the ICER per person is lower than the GNP per person, then the cost-effectiveness of intervention is too high. If the ICER is 1–3

times higher than the GNP per person, then the cost is effective, and in the case of 3 times or higher the cost is not effective (5).

In accordance with the WHO, when we accept GNP as the threshold basis, the value for 2012 GNP per person is taken as 18,927 TL (6). Thus, 18,927 TL and less is assessed as highly cost-effective, whereas up to 56,781 TL is considered only as cost-effective. The ICER found is higher than the threshold values, thus suggesting that pemetrexed/cisplatin treatment is not cost-effective in the first phase treatment of advanced-stage NSCLC.

3.4. Sensitivity analysis results

For the purpose of determining whether certain variables influence the cost-effectiveness analysis results, one-way sensitivity analyses were conducted. Table 4 exhibits the sensitivity analysis results.

Table 4. One-way sensitivity analysis results.

Variable	Variation	Incremental cost effectiveness ratio (ICER) (TL/QALY)
Pemetrexed cost	Decreased 10%	184,767
	Decreased 20%	148,789
	Decreased 30%	112,810
	Decreased 40%	76,832
Reduction ratio	0%	222,784
	1%	222,089
	2%	221,413
	4%	220,111
	5%	219,483
	6%	218,871
Cost calculations	Per average	220,283
Effectiveness data	Weighted according to British standards	198,054
Time period	45 months	219,430

When critical variable values are modified, the ICER oscillates between 76,832 TL and 222,784 TL. However, under all circumstances the pemetrexed/cisplatin treatment in advanced stage NSCLC has been found higher than the ICER threshold determined; thus, it was identified as not cost-effective.

3.5. Budgetary impact analysis results

In order to examine the budgetary effect of medications and their fundability, budgetary impact analysis was conducted. For budgetary impact analysis, the target population of advanced stage NSCLC in Turkey was used. The data were taken from the study of Göksel et al. (7). According to 2008 data, the number of annually expected cases in Turkey is 30,239. The NSCLC rate is 82.2%, advanced stage NSCLC rate is 72.6%, and the rate of patients receiving chemotherapy is 48%. Budgetary impact analysis results are given in Table 5.

The budgetary impact of pemetrexed/cisplatin in first phase treatment of advanced-stage NSCLC has been calculated as 154,038,866 TL. On the other hand,

Table 5. Budget impact analysis.

	Budget impact (TL)
Pemetrexed/cisplatin	154,038,866
Gemcitabine/cisplatin	89,629,372

gemcitabine/cisplatin exhibited an impact valued of 89,629,372 TL for the same cancer condition.

4. Discussion

Cost-effectiveness of pemetrexed/cisplatin and gemcitabine/cisplatin first phase treatments were published in 2010 by NICE. According to the NICE Assessment Board, the pemetrexed/cisplatin treatment was found to be cost-effective. However, the Board also clearly indicated that the availability of gemcitabine treatment generics and subsequent decline in prices will result in an inability of the pemetrexed/cisplatin treatment to protect its cost-effectiveness (8).

In Turkey, an approximate 35% price drop was experienced from 2010 onwards as a result of the market availability of gemcitabine active ingredient and generic medications. Our study, conducted after the entry of generic drugs into the market, has found pemetrexed/cisplatin treatment as not cost-effective, and this is in accordance with the NICE report expectations.

Studies that compared gemcitabine to other medications used for the first phase of advanced-stage NSCLC found it to be cost-effective. In brief, Evans assessed the gemcitabine active ingredient as cost-effective against the best support care (9). Clegg et al. demonstrated that vinorelbine, vinorelbine/cisplatin, and gemcitabine regimens had the lowest added cost compared to best support care (10). Lees et al. evaluated gemcitabine or gemcitabine/cisplatin

use as cost-effective in advanced stage NSCLC compared to best supportive care, standard care, or new generation medications (11). Szczepura reviewed studies that performed an economic assessment of gemcitabine and concluded that gemcitabine is cost-effective against the standard and new treatments (12). Furthermore, in a sensitivity study conducted by Uyl-de Groot et al. on advanced stage NSCLC patients, the gemcitabine/cisplatin treatment was found to have superior cost-effectiveness in comparison to new alternative medication (13). A cost-effectiveness literature review study examined the gemcitabine active ingredient both as a singular agent and as a cisplatin combination within the context of NSCLC, breast cancer, uterine cancer, and pancreatic cancer (14). Cost-effectiveness studies demonstrated that the gemcitabine/cisplatin combination was cost-favorable in NSCLC treatment depending on the differing national health care perspectives. The shared conclusion of all these studies is that the cost-effectiveness superiority of gemcitabine/cisplatin in advanced stage NSCLC treatment as compared to other treatments supports our finding that pemetrexed/cisplatin treatment is not superior to gemcitabine/cisplatin.

In this study, advanced stage NSCLC patients were examined and no histological discrimination was exercised. In future studies utilizing histological approaches we anticipate different results. However, this study, based on a literature survey, compared the docetaxel, paclitaxel, vinorelbine, gemcitabine, and pemetrexed treatments in the first phase of advanced stage NSCLC treatment, and erlotinib and gefitinib were compared in the second phase of the treatment. Although pemetrexed/cisplatin treatments in first phase advanced stage NSCLC were observed to be optimal for nonsquamous patients, the gemcitabine/cisplatin treatment was found cost-effective, whereas erlotinib was found to be cost-effective for the second phase treatment (15).

In phase III of the study, equal survivability of 10.3 months for both pemetrexed/cisplatin and gemcitabine/cisplatin treatments was found (16). Our study found equal survivability of 9.9 months in Turkey for both treatments of advanced stage NSCLC.

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When considering the present study and previous studies jointly, it is suggested that the comparison of cost-effectiveness studies involving different aims, methodologies, medications compared, data collection methods, and the widely varying costs does not offer a fitting context for the evaluation of the results obtained.

However, when the subject is considered in terms of medication policies in Turkey, it is deemed that gemcitabine/cisplatin treatment, which is found in the refund list, is a better choice for advanced stage NSCLC.

Although decision makers contemplating repayment list inclusion of medications previously considered the handles named first, second, and third in terms of clinical efficiency, reliability, and quality, now they are in need of data for the fourth and fifth, i.e. cost-effectiveness and affordability.

In order to effectively utilize limited health resources and decide which health technology will be refunded, the use of economic modeling is increasingly favored. In this study, the Markov model was used to assess the cost-effectiveness of pemetrexed/cisplatin and gemcitabine/cisplatin first phase treatments of advanced stage NSCLC from the perspective of the Social Security Institution in Turkey.

According to the results of the present study, the cost per gained extra QALY by pemetrexed/cisplatin treatment of first phase advanced stage NSCLC is found to be 220,754 TL. When this value is compared with GNP per person, the use of pemetrexed/cisplatin treatment is not seen as cost-effective in the first phase of advanced-stage NSCLC. However, the active role of generic drugs in the market and reduced medication costs may tilt the cost-effectiveness equation in favor of pemetrexed/cisplatin.

Acknowledgment

This study was supported by a PhD thesis grant of the Scientific Research Projects Coordination Unit of Hacettepe University (Grant No: 09.T02.102.001). For this study permission from the Nonintrusive Clinical Research Ethics Board of Hacettepe University was obtained.

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