Advances in Pharmacoepidemiology & Drug Safety

Ohno et al., Adv Pharmacoepidem Drug Safety 2013, 2:3
DOI: 10.4172/2167-1052.1000133

Research Article Open Access

A Survey of Non-Small Cell Lung Cancer Patients with Meningeal Carcinomatosis in Japan: Incidence and Medical Resource Consumption

Shinya Ohno, Shiro Hinotsu, Kyoko Murata, Shiro Tanaka and Koji Kawakami*

Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Japan

Abstract

Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) may be effective for patients for non-small cell lung cancer (NSCLC) with meningeal carcinomatosis (MC), but evidence is limited particularly for the economics aspects. This study aimed to estimate the incidence of MC and resource consumption for NSCLC patients with MC as an exploratory study for further pharmacoeconomic evaluation of EGFR-TKI treatment in these patients.

Methods: Patients diagnosed with NSCLC in Kyoto University Hospital between January 1, 2005 and December 31, 2008 was identified using medical record data in the hospital. The cumulative incidence of MC was calculated taking into account the competing risk of death. The economic analysis adopted the payer perspective and included direct medical costs (2010 costs) from the date of diagnosis of MC until the time of death. The resource utilization data are expressed as costs per patient per month.

Results: Of 376 patients diagnosed with NSCLC in the study period, 28 were diagnosed with MC up to December 31, 2009 and the cumulative incidences at 1 and 2 years after NSCLC diagnosis were 2.4% and 6.0% respectively. The drug costs per patient per month in MC patients treated with an EGFR-TKI were more than twice that in the non-EGFR-TKI group, but the total costs per patient per month were lower in the EGFR-TKI group. A comparison of sub-categories of costs showed that hospitalization accounted for the highest percentage of medical resource consumption.

Conclusions: These estimates constitute a basis for cost-effectiveness analysis of EGFR-TKI treatment for NSCLC patients.

Keywords: Meningeal carcinomatosis; Interstitial pneumonia; Radiotherapy

Background

Lung cancer was the second most common cancer in Japanese men males and the fourth most common in Japanese women females in 2005, and the leading cause of cancer-related deaths in men and women in 2009. Lung cancer is generally classified into two types based on histology: non-small cell lung cancer (NSCLC) and small cell lung cancer. The majority (85%) of new cases of lung cancer are NSCLC [1,2].

Meningeal carcinomatosis (MC) is a rare neurologic complication that occurs in approximately 5% of patients with cancer [3] and 1.4% of patients with NSCLC [4]. MC causes severe symptoms such as vomiting, headache, and neurological sequela, and often requires hospitalization and medication. The prognosis of patients with NSCLC and MC remains poor, with a median survival time (MST) without treatment of about 4-6 weeks [5]. The treatment options include radiotherapy, systemic chemotherapy, and intrathecal chemotherapy with methotrexate, thiotepa, and cytarabine [6]. However, the effectiveness of these treatments is limited and MST is only extended to about 2-3 months [7].

Gefitinib and erlotinib are small molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Several recent case reports have demonstrated the effectiveness of EGFR-TKI for NSCLC patients with MC [8-10], but there are no data on the health economics of treatment for MC. Therefore, the purpose of this study was to estimate the incidence of MC in NSCLC patients and the costs associated with treatment of these patients.

Patients and Methods

Study population and clinical data collection

A retrospective analysis of medical record data identified a total of 376 consecutive patients with cytologically or histologically proven NSCLC at Kyoto University Hospital between January 1, 2005 and December 31, 2008. Clinical data were collected for gender, age at diagnosis of NSCLC and MC, smoking status, EGFR mutation, Eastern Cooperative Oncology Group (ECOG) performance status at the time of diagnosis of NSCLC and MC, histology of lung cancer, metastatic sites at the time of diagnosis of MC, number of chemotherapy regimens received before diagnosis of MC, history of whole brain radiotherapy before diagnosis of MC, interval between diagnosis of lung cancer and MC, lengths of hospitalization after diagnosis of MC, types and numbers of cycles of radiotherapy, and detailed information on drug treatment and other therapy.

The research protocol was approved by the Ethics Committee,

***Corresponding author:** Koji Kawakami, M.D., PhD., Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto, 606-8501, Japan; E-mail: kawakami.koji.4e@kyoto-u.ac.jp

Received April 26, 2013; **Accepted** May 22, 2013; **Published** May 24, 2013

Citation: Ohno S, Hinotsu S, Murata K, Tanaka S, Kawakami K (2013) A Survey of Non-Small Cell Lung Cancer Patients with Meningeal Carcinomatosis in Japan: Incidence and Medical Resource Consumption. Adv Pharmacoepidem Drug Safety 2: 133. doi:10.4172/2167-1052.1000133

Kyoto University Graduate School and Faculty of Medicine. This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research in Japan. JMP, version 8.0.1 (SAS Institute, Cary, NC, USA) [11] was used for all statistical analyses.

Incidence of meningeal carcinomatosis

The potential follow-up period for each patient was at least 1 year from diagnosis of NSCLC. Diagnosis of MC was proven by detection of malignant cells in cerebrospinal fluid in microscopic cytology or typical findings in magnetic resonance imaging (MRI). The starting date of the analysis was defined as the day of diagnosis of NSCLC and the event day was defined as the day of diagnosis of MC. Survival cases were defined based on the last confirmed day of survival and untraceable cases were defined using the last confirmed day of survival before follow-up ended. The cumulative incidence of MC was calculated taking into account the competing risk of death. The cumulative incidence of MC was calculated for all NSCLC patients and for subgroups of NSCLC patients with a diagnosis of stage IIIB or IV and histology of adenocarcinoma considering the treatment with an EGFR-TKI before diagnosis of MC.

Cost analysis

The patients with MC were followed-up until October 1, 2010. The evaluation of medical resource consumption adopted the payer perspective and included direct medical costs from the diagnosis of MC until the time of death. Indirect costs (e.g. lost income) and intangible costs (e.g. pain and suffering) were not assessed. Direct medical costs were analyzed using a medical service fee table and the national health insurance drug price table (2010 edition). No discounting was used as the treatment duration in most cases was less than one year. A direct cost comparison was performed between patients treated with and without an EGFR-TKI after diagnosis of MC. To adjust for differences in time, resource utilization data are expressed as costs (yen) per patient per month.

Total costs were defined as all costs in the analysis and were classified into six items depending on the fee-for-service and therapeutic purpose: basic medical care and management, home care, and dietary medical expenses and hospitalization were defined as "Hospitalization and outpatient costs; costs of medication and injections as "drug costs"; costs of medical treatment and surgery as "treatment / surgery costs"; costs of blood test and imaging as "examination costs"; costs of radiotherapy as "radiologic treatment costs", and other expenses as "other costs". These six components were added to give the total costs. Drug costs included only the costs of pharmaceuticals used for treatment [12]. Examination costs included those for drug and contrast media used in an examination.

Results

Patient characteristics

The characteristics of all the patients with NSCLC and those also diagnosed with MC are shown in Table 1. There were more male patients in both of these populations and adenocarcinoma was the most common histological type, followed by squamous cell carcinoma. Most patients diagnosed with MC were at an advanced NSCLC stage of IIIB or IV. The smoking rate was 73% in all patients, but only 54% in patients diagnosed with MC. EGFR mutations were found in 36% of patients diagnosed with MC, which is somewhat high, but the accuracy of this proportion is unclear because the test was not performed in 60% of the patients.

	All NSCLC patients (n=376)	MC patients (n=28)
Gender		
Male	274 (72.9%)	17 (60.7%)
Female	102 (27.1%)	11 (39.3%)
Age (median, range)	65 (29-85)	57.5 (35-76)
Histological type		
Adenocarcinoma	232 (61.7%)	26 (92.8%)
Squamous cell carcinoma	77 (20.5%)	1 (3.6%)
Large-cell carcinoma	17 (4.5%)	0 (0%)
Others	50 (13.3%)	1 (3.6%)
Stage		
I	43 (11.4%)	2 (7.1%)
II	31 (8.2%)	1 (3.6%)
IIIA	48 (12.8%)	2 (7.1%)
IIIB	97 (25.8%)	5 (17.9%)
IV	157 (41.8%)	18 (64.3%)
Smoking status		
Former	273 (72.6%)	15 (53.6%)
Never	103 (27.4%)	13 (46.4%)
ECOG performance status		
0-1	367 (97.6%)	28 (100%)
2-4	9 (2.4%)	0 (0%)
EGFR mutation		
Positive	51 (13.6%)	10 (35.7%)
Negative	51 (13.6%)	1 (3.6%)
Unknown	274 (72.9%)	17 (60.7%)

*NSCLC: Non-Small-Cell Lung Cancer, MC: Meningeal Carcinomatosis, ECOG: Eastern Cooperative Oncology Group, EGFR: Epidermal Growth Factor Receptor

Table 1: Characteristics of all NSCLC patients and patients with MC.

Age (median, range)	60 (36-79)
ECOG performance status	
0-1	19 (67.9%)
2-4	9 (32.1%)
Systemic metastasis at	
Diagnosis of MC	
Brain (past, same time)	16 (57.1%), 8 (28.6%)
Bone	15 (53.6%)
Lung to lung	8 (28.6%)
Adrenal gland	4 (14.3%)
Liver	4 (14.3%)
Days between diagnosis of	
lung cancer and MC, (median, range)	490 (22-1520)
Previous whole brain radiation therapy	9 (32.1%)
Previous EGFR-TKI	14 (50.0%)
Symptoms and Signs	
Kernig's sign	13 (46.4%)
Headache	12 (42.9%)
Nausea, vomiting	10 (35.7%)
Unstable gait	11 (39.3%)

*MC: Meningeal Carcinomatosis, ECOG: Eastern Cooperative Oncology Group, EGFR-TKI: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor

Table 2: Characteristics 28 MC patients at the time of diagnosis.

The characteristics of the patients at the time of diagnosis of MC are shown in Table 2. The median age of the 28 patients was 60 years old, with a range of 36 to 79 years old. Performance status (PS) was 0-1 for these patients at the time of diagnosis of NSCLC, but PS in 16 of these patients had deteriorated at the time of diagnosis of MC. Of the 28 patients, 24 had radiological evidence or a history of brain metastases;

8 had concurrent diagnoses of brain metastases and MC; and 16 had a history of brain metastases, of which 9 had received whole brain irradiation before diagnosis of MC. Fourteen patients had a history of treatment with an EGFR-TKI before diagnosis of MC. The median interval between the diagnoses of lung cancer and MC was 490 days, with a range of 22-1520 days.

Incidence of MC

The follow-up rates at 1-year and 2-year were 99.5% and 86.7%, respectively. The cumulative incidences of MC calculated taking account of the competing risk of death were estimated to be 2.4% and 6.0% at 1 and 2 years after diagnosis of NSCLC, respectively (Figure 1). In subgroup analyses, these respective incidences were 3.0% and 8.4% in 232 patients with adenocarcinoma, 3.44% and 7.92% in 254 patients with stage IIIB or IV NSCLC, 2.96% and 8.54% in 102 patients with stage IIIB or IV NSCLC treated with an EGFR-TKI, and 3.60% and 7.29% in 152 patients with stage IIIB or IV NSCLC who did not receive an EGFR-TKI (Figure 2).

Cost analysis

Among the 28 patients with MC, economic data for nine were incomplete because of hospital transfer. Therefore, use of medical resources was evaluated for 19 cases, for which the characteristics, treatment history and treatment after diagnosis of MC are shown in Table 3. These patients were divided into those treated with (EGFR-TKI group) or without (non-EGFR-TKI group) an EGFR-TKI after diagnosis of MC. The median survival times after diagnosis of MC were 127 days in the EGFR-TKI group and 40 days in the non-EGFR-TKI group. The EGFR-TKI group was younger and had a better PS compared with the non-EGFR-TKI group.

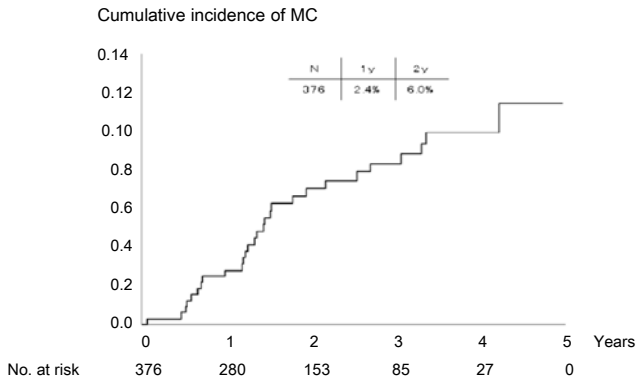

Figure 1: Cumulative incidence of MC in all eligible patients.

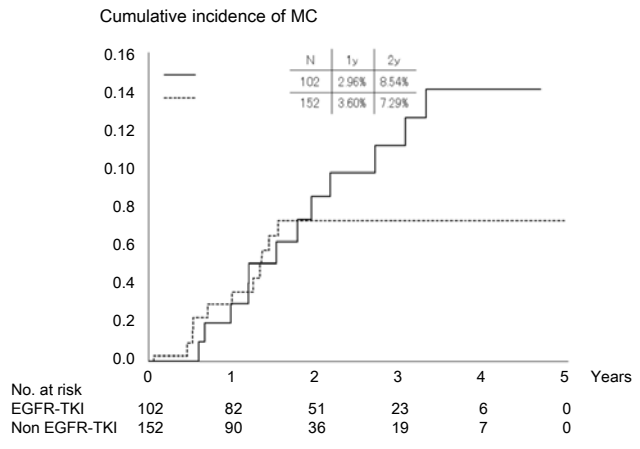

Figure 2: Cumulative incidence of MC in stage IIIB or IV NSCLC patients with and without treatment with EGFR-TKI.

The median and range of total costs per patient per month were 706,607 (¥1,371,110-¥246,601) yen in the EGFR-TKI group and 1,033,361 (¥1,143,610-¥680,244) yen in the non-EGFR-TKI group (Table 4). Especially, there was a strong relationship between hospitalization costs and total costs.

Drug costs were more than twofold higher in the EGFR-TKI group compared to the non-EGFR-TKI group. Excluding "Hospitalization and outpatient costs", the median and range costs per month per person were ¥361,519 (¥679,097-¥212,826) yen in the EGFR-TKI group and ¥287,733 (¥384,651-¥188,598) yen in the non-EGFR-TKI group. Management of increased intracranial pressure and pain control were performed for most cases. There was no case of drug-induced interstitial pneumonia. The median cost for infection was higher in the EGFR-TKI group, whereas the median cost of the treatment for nausea and vomiting was higher in the non-EGFR-TKI group.

Discussion

MC develops in 5-8% of solid cancer cases, with most of these cases having a histologic type of adenocarcinoma. In the current study in 376 patients diagnosed with NSCLC, the histologic type was adenocarcinoma in 26 of 28 patients who developed MC and the risk of MC was similar to that previously reported [13,14]. The cumulative incidence of MC in all NSCLC patients was calculated taking into account death as a competing risk, but the value may have been underestimated because there were some patients in whom test for confirmation could not be performed due to severe systemic conditions, despite clinical findings indicating a strong suspicion of MC, and patients diagnosed based on CT alone were excluded. Our findings also suggested that treatment of NSCLC with an EGFR-TKI is a risk for development of MC. However, many patients who developed MC had also brain metastasis, which might be a risk factor for MC. Many recent reports have suggested the efficacy of an EGFR-TKI for brain metastasis and these drugs may have been used selectively for patients with brain metastasis. Therefore, further investigation of the association between use of EGFR-TKI and development of MC is necessary.

Regarding resource consumption after development of MC, the mean total cost per patient per month was lower for EGFR-TKI-treated patients. The cost for anticancer drugs accounted for more than half of the drug costs in the EGFR-TKI group. In Japan, it will be difficult to use biosimilar of EGFR-TKI, this trend of cost would be continuing in near future [15]. Glycerol and steroids were mainly used for the control of intracranial pressure control and accounted for the second largest cost following the cost of transfusion in the non-EGFR-TKI group. The cost for pain control differed markedly between the groups, suggesting that this cost is strongly dependent on the patient condition. Measures against constipation were taken in many patients, but these did not have a marked influence on costs. Skin eruption is a frequent adverse event in EGFR-TKI-treated patients and was expected to result in a marked difference in costs for skin control, but there was no major difference in these costs between the two groups. The costs for antiemetic treatment and sedation were higher in the non-EGFR-TKI group. Since many patients with relatively poor conditions were included in the non-EGFR-TKI group, the incidence of severe neurological symptoms may also have been high. Regarding infection, the incidence of infectious

Patient Number	Patient Background					Prior treatment of MC		Treatment after diagnosis of MC				Survival days after diagnosis of MC
	Gender	Age	PS	Stage	Histology	EGFR-TKI	Whole brain radiation therapy	Chemotherapy	Whole brain radiation therapy	Other r adiation	Administration days of EGFR-TKI	
1	M	60	0	IV	Adenocarcinoma	No	No	No	No	No	35	51
2	F	50	0	IV	Adenocarcinoma	No	No	Yes	Yes	Chest	343	732
3	M	64	3	IV	Adenocarcinoma	No	Yes	No	No	Supine	4	45
4	M	49	1	IV	Adenocarcinoma	No	Yes	No	No	No	48	90
5	M	56	1	IIIB	Adenocarcinoma	No	No	No	No	No	3	30
6	F	58	1	IIIA	Squamous cell carcinoma	Yes	No	Yes	Yes	No	135	164
7	M	54	1	IV	Adenocarcinoma	Yes	No	Yes	Yes	Lumbar vertebra, lymph node	170	439
8	F	68	0	IV	Adenocarcinoma	Yes	Yes	No	No	No	12	69
9	F	55	0	IV	Adenocarcinoma	Yes	No	Yes	Yes	No	207	448
10	M	36	1	IV	Adenocarcinoma	Yes	No	Yes	Yes	No	185	194
11	M	48	1	IIIA	Adenocarcinoma	No	Yes	No	No	No		37
12	M	66	2	IV	Adenocarcinoma	No	No	No	Yes	No		43
13	F	61	3	IV	Adenocarcinoma	No	No	No	Yes	No		12
14	M	58	1	IV	Adenocarcinoma	No	Yes	No	No	No		41
15	M	61	2	IV	Adenocarcinoma	No	No	No	Yes	No		40
16	F	56	2	IV	Adenocarcinoma	No	No	No	Yes	No		21
17	F	79	1	IIIB	Adenocarcinoma	Yes	No	No	Yes	No		36
18	F	56	2	IV	Adenocarcinoma	Yes	No	Yes	Yes	Cervival vertebra		40
19	M	77	0	IV	Adenocarcinoma	Yes	No	No	Yes	No		48

*MC: Meningeal Carcinomatosis, EGFR-TKI: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor

Table 3:

		EGFR-TKI (n=10)			No EGFR-TKI (n=9)		
		Median	Max	Min	Median	Max	Min
Total cost per month		¥706,607	¥1,371,110	¥246,601	¥1,033,361	¥1,143,610	¥680,244
Hospitalization and outpatient costs		¥319,306	¥692,013	¥14,339	¥645,805	¥738,657	¥411,729
Drug costs	**Subtotal**	¥240,602	¥449,104	¥130,147	¥123,566	¥187,288	¥64,400
Anti-cancer drug		¥125,174	¥281,257	¥17,025	¥0	¥35,593	¥0
EGFR-TKI		¥99,885	¥161,900	¥17,025	¥0	¥0	¥0
Management of ICP		¥5,171	¥42,612	¥0	¥16,885	¥46,500	¥0
Pain control		¥6,075	¥106,131	¥352	¥11,516	¥140,722	¥3,052
Neurological symptoms		¥501	¥4,268	¥0	¥3,633	¥12,803	¥126
Constipation control		¥302	¥2,561	¥0	¥312	¥1,568	¥0
Fluid		¥9,619	¥71,204	¥558	¥22,135	¥41,320	¥6,931
Skin eruption		¥576	¥2,781	¥96	¥144	¥6,323	¥0
Nausea and vomiting		¥386	¥7,739	¥0	¥925	¥9,444	¥0
Gastric ulcer		¥4,083	¥24,842	¥256	¥6,917	¥23,267	¥0
Infection (e.g. pneumonia)		¥8,818	¥197,690	¥0	¥0	¥23,573	¥0
Others		¥3,771	¥107,885	¥0	¥0	¥12,656	¥0
Technical fees and adding, etc		¥13,897	¥53,526	¥3,844	¥28,038	¥44,684	¥4,307
Treatment/surgery costs	**Subtotal**	¥9,571	¥34,131	¥173	¥8,299	¥35,220	¥616
Oxygen		¥648	¥12,502	¥0	¥1,832	¥6,335	¥0
Sputum suction		¥248	¥12,209	¥0	¥1,964	¥15,508	¥0
Others		¥5,020	¥28,084	¥0	¥2,353	¥16,001	¥0
Examination costs	**Subtotal**	¥99,025	¥217,363	¥44,209	¥122,497	¥177,557	¥85,692
Blood testing		¥38,810	¥80,377	¥10,692	¥50,242	¥73,800	¥41,100
Imaging		¥54,291	¥170,098	¥32,869	¥73,384	¥127,314	¥37,323
Computed tomography		¥36,994	¥84,139	¥19,754	¥51,910	¥90,824	¥26,834
X-ray		¥3,666	¥14,308	¥1,380	¥6,955	¥16,098	¥0
Nuclear medicine		¥3,414	¥77,371	¥0	¥0	¥63,592	¥0
Others		¥4,399	¥5,896	¥1,151	¥3,372	¥5,957	¥0
Radiologic treatment costs	**Subtotal**	¥18,491	¥72,391	¥0	¥100,024	¥240,409	¥0
Other costs	**Subtotal**	¥4,962	¥43,698	¥140	¥7,827	¥27,281	¥4,837
Physical therapy		¥0	¥40,236	¥0	¥0	¥12,203	¥0
Miscellaneous		¥3,938	¥10,161	¥140	¥7,827	¥21,210	¥1,286

*EGFR-TKI: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor

Table 4: Cost per patient.

disease complication was high in the EGFR-TKI group and the cost for control against infection was also high. Therefore, these costs for infection and for anticancer drugs should be considered in calculating the costs for treatment of MC.

In the 28 MC patients, the median survival times were 164 days (8-16 weeks) for those treated with an EGFR-TKI and 40 days (4-6 weeks) for those who did not receive an EGFR-TKI. Therefore, the prognosis of MC was very poor [16], but the survival time was longer for EGFR-TKI-treated patients, as also found in previous studies, and 3 of these patients survived for longer than one year after diagnosis. However, PS and the presence or absence of serious neurological symptoms and metastasis in other organs are strong prognostic factors [17]. PS was 0-1 in many EGFR-TKI-treated patients and it is possible that EGFR-TKI administration was biased to patients in a relatively good condition for whom long-term survival could be expected.

Several limitations of the study warrant mention. First, this is an observational study which cannot exclude potential of confounding bias, so prescription could not be controlled and direct comparison between EGFR-TKI and non-EGFR-TKI groups may be difficult. Moreover, the patients were treated at a single institution and the sample size was small, suggesting the presence of a selection bias in analyzed cases. For evaluation of resource consumption, the 2010 payments for medical services and standard prices for medicines were used to calculate the cost. The drug price is reduced in revision in every 2 years, leading to potential of over estimation of costs. However, recent revisions do not have much impact. The analysis was also performed from the payer's viewpoint and only direct medical expenditure was investigated. It may also be necessary to evaluate the cost from a social point of view with inclusion of direct non-medical expenditures and associated costs for a relatively serious disease such as MC, including transportation expenses and time-costs for unpaid caregivers. Another concern is that EGFR testing was not performed in 60% of the patients, which is substantially different from the current clinical practice.

Conclusions

The estimated incidences of MC at 1 and 2 years after NSCLC diagnosis were 2.4% and 6.0%, respectively. The costs of hospitalization accounted for the highest percentage of medical resource consumption for patients with MC. These estimates constitute a basis for cost-effectiveness analysis of EGFR-TKI treatment for NSCLC patients.

References

1. Sher T, Dy GK, Adjei AA (2008) Small cell lung cancer. Mayo Clin Proc 83: 355-367.
2. Travis WD, Travis LB, Devesa SS (1995) Lung cancer. Cancer 75: 191-202.
3. Larson DA, Rubenstein JL, Mcdermott MW (2005) Carcinomatous meningitis. Cancer principles and practice of oncology. 7th ed. Philadelphia: Lippincott, Williams and Wilkins 2333-2335.
4. Kimura K, Sakai H, Sumimoto H, Hibino S, Goto I, et al. (1996) Leptomeningeal carcinomatosis in patients with lung cancer. Jpn J Lung Cancer 36: 879-883.
5. Grossman SA, Krabak MJ (1999) Leptomeningeal carcinomatosis. Cancer Treat Rev 25: 103-119.
6. Grossman SA, Finkelstein DM, Ruckdeschel JC, Trump DL, Moynihan T, et al. (1993) Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. J Clin Oncol 11: 561-569.
7. Wasserstrom WR, Glass JP, Posner JB (1982) Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. Cancer 49: 759-772.
8. Kim MK, Lee KH, Lee JK, Choi JH, Hyun MS (2005) Gefitinib is also active for carcinomatous meningitis in NSCLC. Lung Cancer 50: 265-269.
9. Hashimoto N, Imaizumi K, Honda T, Kawabe T, Nagasaka T, et al. (2006) Successful re-treatment with gefitinib for carcinomatous meningitis as disease recurrence of non-small-cell lung cancer. Lung Cancer 53: 387-390.
10. Sakai M, Ishikawa S, Ito H, Ozawa Y, Yamamoto T, et al. (2006) Carcinomatous meningitis from non-small-cell lung cancer responding to gefitinib. Int J Clin Oncol 11: 243-245.
11. Jmp 8 Introductory Guide, SAS Institute, 2008.
12. Hamada S, Hinotsu S, Hori K, Furuse H, Oikawa T, et al. (2012) The cost of antiemetic therapy for chemotherapy-induced nausea and vomiting in patients receiving platinum-containing regimens in daily practice in Japan: a retrospective study. Support Care Cancer 20: 813-820.
13. Sudo J, Honmura Y, Kurimoto F, Komagata H, Sakai H, et al. (2006) [Meningeal carcinomatosis in patients with lung cancer]. Nihon Kokyuki Gakkai Zasshi 44: 795-799.
14. Grossman SA, Krabak MJ (1999) Leptomeningeal carcinomatosis. Cancer Treat Rev 25: 103-119.
15. Horikawa H, Tsubouchi M, Kawakami K (2009) Industry views of biosimilar development in Japan. Health Policy 91: 189-194.
16. Groves MD (2011) Leptomeningeal disease. Neurosurg Clin N Am 22: 67-78, vii.
17. Waki F, Ando M, Takashima A, Yonemori K, Nokihara H, et al. (2009) Prognostic factors and clinical outcomes in patients with leptomeningeal metastasis from solid tumors. J Neurooncol 93: 205-212.