Chemotherapy beyond first-line in stage IV metastatic non-small cell lung cancer

Riad Naim Younes[1], José Rodrigues Pereira[2], Abdo Latif Fares[3], Jefferson Luiz Gross[4]

[1] Full Professor, Department of Surgery, Faculdade de Medicina, Universidade de São Paulo (FMUSP); Physician at Hospital Sírio-Libanês and Centro de Oncologia, Hospital São José (Beneficência Portuguesa-SP), São Paulo, SP, Brazil
[2] Pneumologist by Sociedade Brasileira de Pneumologia e Tisiologia (SBPT); Director-president, Instituto Brasileiro de Cancerologia Torácica (IBCT); Physician at Hospital São José (Beneficência Portuguesa-SP) and Santa Casa de Misericórdia de São Paulo (ISCMSP), São Paulo, SP, Brazil
[3] Graduate Student, Faculdade de Ciências Médicas, Santa Casa de São Paulo, São Paulo, SP, Brazil
[4] MSc and PhD in Medicine, FMUSP; Physician at Hospital AC Camargo and Hospital Sírio-Libanês, São Paulo, SP, Brazil

Summary

Objective: Platinum-based doublet chemotherapy is considered the standard of care for advanced non-small cell lung cancer (NSCLC). However, prognosis after recurrent or progressive disease following first-line chemotherapy is usually poor. Maintenance chemotherapy, second line treatment and even third line chemotherapy are available for patients with advanced NSCLC. Unfortunately, few patients are candidates for chemotherapy beyond first line. The present study evaluated characteristics of patients with NSCLC and outcomes of the treatment of their metastatic disease, with emphasis on second and third-line chemotherapy. **Methods:** This was a retrospective observational study of 2,673 patients with metastatic, stage IV, non-small cell lung cancer admitted for treatment in two São Paulo institutions. First-line chemotherapy was defined as the first chemotherapeutic approach administered to the patient. Second and third-line chemotherapy were defined as the systemic treatment administered after discontinuing first-line chemotherapy, either for intolerance or for progressive or recurrent disease. **Results:** Most patients (57.9%) received first-line chemotherapy, and approximately 23.4% received second-line and 8% third-line regimens. Only 2.5% received fourth-line chemotherapy. Median overall survival (OS) was 8 months (95% CI: 8-9 months). At univariate analyses, gender ($p < 0.05$), histology, first-line chemotherapy, objective response to first-line chemotherapy and second-line chemotherapy ($p < 0.01$) were prognostic factors related to overall survival. At multivariate analysis, only performance status ($p = 0.04$), receiving any second-line chemotherapy ($p < 0.01$) and response to first-line chemotherapy ($p < 0.01$) were independent predictors of overall survival. **Conclusion:** Second-line chemotherapy is a therapeutic strategy that should be considered for a selected group of patients. Performance status and response to first-line chemotherapy could be determinant characteristics to select patients who might be treated beyond first-line chemotherapy.

Keywords: Carcinoma, non-small-cell lung; neoplasm metastasis; antineoplastic combined chemotherapy protocols; drug therapy; lung neoplasms.

Study conducted at Hospital AC Camargo, Instituto Arnaldo Vieira de Carvalho (IAVC) and Hospital São José, São Paulo, SP, Brazil

Submitted on: 05/30/2011
Approved on: 09/24/2011

Financial Support:
Partial grant from Sanofi-Aventis, São Paulo, SP, Brazil

Correspondence to:
Riad Naim Younes
Rua Dona Adma Jafet, 50
4º andar, cjs. 41/43 – Bela Vista
CEP: 01308-050
São Paulo, SP, Brazil
Phone: +55 (11) 3257-2808
rnyounes@yahoo.com

Conflict of interest: None.

©2011 Elsevier Editora Ltda.
Todos os direitos reservados.

Resumo

Quimioterapia em câncer de pulmão não pequenas células metastático estádio IV: além da primeira linha

Objetivo: A quimioterapia dupla com base em platina consiste no tratamento padrão para o câncer de pulmão não pequenas células (CPNPC) avançado. Contudo, o prognóstico dos pacientes com doença recorrente ou em progressão após a quimioterapia de primeira linha é ruim. Quimioterapia de manutenção, de segunda linha e até de terceira linha são tratamentos válidos para pacientes com CPNPC de estádio avançado. Infelizmente, poucos pacientes são candidatos para o tratamento quimioterápico além daquele de primeira linha. O presente estudo avalia as características de pacientes com CPNPC e os resultados do tratamento da doença metastática, com ênfase na quimioterapia de segunda e de terceira linha. **Métodos:** Este é um estudo observacional e retrospectivo de 2.673 pacientes com CPNPC metastático, estádio IV, admitidos para tratamento em duas instituições de São Paulo, SP. A quimioterapia de primeira linha foi definida como a primeira abordagem quimioterápica administrada ao paciente. Quimioterapias de segunda e de terceira linha foram definidas como tratamento sistêmico administrado após a interrupção da quimioterapia de primeira linha, seja por intolerância ou por doença em progressão ou recorrente. **Resultados:** A maioria dos pacientes (57,9%) foi submetida à quimioterapia de primeira linha; aproximadamente 23,4% receberam quimioterapia de segunda linha e 8% de terceira. Apenas 2,5% foram submetidos ao regime de quarta linha. A sobrevida global mediana (OS) foi de 8 meses (IC 95%: 8-9 meses). Na análise univariada, sexo ($p < 0,05$), histologia, quimioterapia de primeira linha, resposta imparcial à quimioterapia de primeira linha e quimioterapia de segunda linha ($p < 0,01$) foram fatores prognósticos relacionados com a sobrevida global. Na análise multivariada, status de performance ($p = 0,04$), submissão do paciente a qualquer tipo de quimioterapia de segunda linha ($p < 0,01$) e resposta à quimioterapia de primeira linha ($p < 0,01$) foram os únicos fatores independentes preditivos de maior sobrevida. **Conclusão:** A quimioterapia de segunda linha é uma estratégia terapêutica a ser considerada em seletos grupos de pacientes. O status de performance e a resposta à quimioterapia de primeira linha poderiam ser alguns dos fatores determinantes durante o processo de seleção dos pacientes que deverão ser submetidos a regimes quimioterápicos além da primeira linha.

Unitermos: Carcinoma pulmonar de células não pequenas; neoplasias pulmonares; quimioterapia.

Introduction

Lung cancer is one of the most common cancers around the world. In 2008, lung cancer was responsible for 13% (1.6 million) of the total cancer cases and 18% (1.4 million) of the cancer deaths[1]. In USA, lung cancer remains the leading cause of cancer-related mortality, with estimated 222,520 new cases and 157,300 deaths anticipated in 2010[2]. In Brazil almost 30.000 new cases were expected to be diagnosed in 2010[3]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all cases[1]. Unfortunately the majority of cases are detected in advanced stage[4]. This is one of the reasons that explain the poor prognosis associated with NSCLC, where nearly 15% of the patients are expected to survive beyond five years from the diagnosis[5-7]. Among patients with metastatic disease the prognosis is dismal. In spite of advances in systemic therapies, the median survival time remains around 12 months[7-9]. Nowadays, platinum-based doublet chemotherapy is considered the standard of care for advanced NSCLC. Results of systemic treatment have shown increasing overall survival as well as better quality of life. However, even with recent advances, most patients present with relapsing or progressive disease after first line chemotherapy. Prognosis after recurrent or progressive disease following first-line chemotherapy is usually poor. Patients who have relapsed after first line chemotherapy and did not receive additional oncologic treatment have a short overall survival, with a median around three months[10]. New drugs, such as pemetrexede, docetaxel and molecular targets agents have been recommended as valid options for second line chemotherapy, with objective response rates around 10%, and significant increase in overall survival, compared to best supportive care[11]. Nowadays, second line chemotherapy is considered standard of care in the treatment of advanced NSCLC[12]. The aims of second line chemotherapy are palliation of symptoms, improvement in quality of life, and increased survival. Although many patients, in this clinical situation, have deteriorated performance status, studies have shown that up to 40% would be candidates to receive second-line chemotherapy[12-14]. The development of new regimens resulted in a significant increase in the total time spent by patients receiving chemotherapy. Maintenance chemotherapy, second line treatment and even third line chemotherapy are available for patients with advanced NSCLC. Due to poor prognosis, physicians should select patients who are adequate candidates to these prolonged treatments, mainly in countries with limited economical resources. Murillo et al.[15] studied the characteristics of chemotherapy given near the end of life to advanced NSCLC patients in a community setting. The authors found that 56% received second line treatment, 26% received third line chemotherapy, 10% received fourth line and 5% received fifth line chemotherapy or greater. The most interesting finding of this study is that almost 50% of the patients received chemotherapy in the last month of life, and 20% received systemic treatment in the last two weeks of the life. This can be explained by the increase demand of patients and their relatives to receive treatment, because they do not accept the inevitability of progressive disease and death. Moreover probably physicians tend to offer chemotherapy to patients that will not have real advantages receiving this treatment, because they are unable to predict life expectancy. Recognition of prognostic factors in patients with advanced NSCLC candidates to receive chemotherapy, mainly second and third lines treatment, is fundamental to avoid futility of therapies. The present study evaluateed patient characteristics of patients with NSCLC, and outcomes of the treatment of their metastatic disease, with emphasis on second and third-line chemotherapy.

Methods

This was a retrospective observational study of patients with metastatic, stage IV, non-small cell lung cancer admitted for treatment in two institutions in São Paulo, Brazil, dedicated to the treatment and research of cancer: Instituto Arnaldo Vieira de Carvalho (IAVC) and Hospital AC Camargo (HACC). The study was approved by the Research Ethical Committee. Clinical data were reviewed from the records of all adult patients from 1990 to 2008. The following inclusion criteria were considered: cytological or histological diagnosis of non-small cell lung cancer; stage IV; and patients admitted for cancer management according to clinical practice guidelines of each institution. According to these inclusion criteria, 2,673 patients were considered for the present study. The following clinical data were obtained by reviewing individual records, registered in a consecutive database: age, gender, performance status, histological type, chemotherapy regimens and status at last follow-up. Performance status was determined by Karnofsky index, according to clinical data available in the records. Classification of clinical staging was obtained from the records, based on clinical notes or reports of imaging exams (chest, upper abdomen CT and brain CT or MRI, and bone scan). First-line chemotherapy was defined as the first chemotherapeutic approach administered to the patient. Second and third-line chemotherapy were defined as the systemic treatment administered after discontinuing first-line chemotherapy, either for intolerance or for progressive or recurrent disease. Status of last follow-up was classified as alive without disease, alive with disease, dead from cancer, dead from other causes, and as lost to follow-up patients who did not return to institution for a period exceeding twice the interval suggested by the assistant physician.

Statistical analysis

The method of Kaplan-Meier was used to determine actuarial survival. Differences in survival were determined by Breslow and log rank analyses. Overall survival time was

defined as the interval between initial diagnosis of NSCLC at each center and the date of last consultation or until death. All statistical analyses were performed with SPSS 10.0 software. The value of $p < 0.05$ was defined as significant.

Results

From 1990 to 2008, 2,673 patients with metastatic stage IV NSCLC had been admitted to either institution (IAVC: 1887, HACC: 786). The median age of the patients on admission was 63 (range 24-89; mean 62.1 ± 2.5). Most patients (1855 – 69.4%) were male. Performance status (KPS) on admission was: < 70 (20.4%), 70 (28.6%), 80 (34.5%), 90 (8.3%), 100 (1.9%), unknown (6.3%). Adenocarcinoma was the leading histologic subtype accounting for 32.9%, followed by squamous-cell carcinoma (30.5%), large-cell undifferentiated carcinoma (26.6%), and unspecified NSCLC (10%). Median follow-up was 9.14 months (range 0-108 months). At the end of our study period, 69.7%, of all patients were dead, while 29.6% were still alive, and 0.7% had no registered information on current status. Most patients (57.9%) received first-line chemotherapy, and approximately 23.4% received second-line and 8% third-line regimens. Only 2.5% received fourth-line chemotherapy. Of the evaluable patients that were submitted to first-line chemotherapy, approximately 61.1% received a platinum-based regimen (cisplatin or carboplatin) and 38.9% a non-platinum-based therapy. Median number of cycles per patient was four (range 1-9). On the other hand, when second-line chemotherapy was administered, approximately 4.9% patients received a platinum-based regimen (cisplatin or carboplatin) and over 95% a non-platinum regimen. The median number of administered cycles per patient was three (range 1-8). Based on the heterogeneity of the drugs used in this clinical setting, detailed data on toxicity were not evaluated in this study. Information about response rates to chemotherapy was determined from the records. The response rate to chemotherapy according to the line of treatment was assessed. Considering all patients submitted to first line of treatment, 79.3% had evaluable information in the records, 1.7% of the evaluable patients had complete response to treatment and 37% partial response, 11.3% had stable disease and 50% progressive disease. From all patients submitted to second line treatment, 81.6% had evaluable information in the records, 0.4% of those had complete response and 10% partial response to treatment, 19.6% had stable disease and 70% progressive disease. Considering all patients that received third line chemotherapy, 83.6% had evaluable information in the records, where no patient presented with documented complete response, while 7% had partial response, 22.4% stable disease, and 70.6% progressive disease.

Median overall survival (OS) was 8 months (95% CI: 8-9 months). As most chemotherapy in second and third lines was administered after the year 2003, we compared overall survival rates in two groups of patients: Those admitted until December 2003 (n = 1,308), and all patients admitted after January 2004 (n = 1,365). There was no statistically significant difference in overall survival between the two groups of patients (median survival: 7.9 months and 8.8 months, respectively, $p = 0.088$).

Univariate analyses of prognostic factors related to overall survival are shown in Table 1. At multivariate analysis, only performance status ($p = 0.04$), receiving any second-line chemotherapy ($p < 0.01$) and response to first-line chemotherapy ($p < 0.01$) were independent predictors

Table 1 – Univariate analysis of overall survival (since admission) according patients characteristics

Variable	Median survival (months)	p (log-rank)	p (Breslow)
Hospital			
IAVC	8	0.06	0.06
HACC	9		
Gender			
Male	8	0.04	0.03
Female	9		
Age			
< 50 years	9	0.13	0.15
50 to 60 years	9		
60 to 70 years	8		
70 to 80 years	8		
> 81 years	6		
Performance status (KPS)			
60	8	0.02	0.30
70	8		
80	9		
90 to 100	8		
Histology			
Squamous cell	8	< 0.01	< 0.01
Adenocarcinoma	8		
Large cell carcinoma	5		
First-line chemotherapy			
Any chemotherapy	11	< 0.01	< 0.01
Best supportive care	4		
Objective response to first-line chemotherapy			
Partial response	17	< 0.01	< 0.01
Stable disease	8		
Progressive disease	3		
Second-line chemotherapy			
Any chemotherapy	17	< 0.01	< 0.01
None	6		
Second-line chemotherapy			
Any chemotherapy	18	< 0.01	< 0.01
None	6		

of overall survival. When all NSCLC patients who received second and/or third-line chemotherapy were considered as a separate group (Figures 1 and 2), overall survival was significantly affected by age (p = 0.021), where patients < 70 years old had a median survival of 19.7 months (range 16-22), compared to 11.3 months (range 8-13.7), and by objective response to first line chemotherapy (p = 0.013). Patients that achieved partial response following first-line chemotherapy presented with median survival of 19.4 months (range 15-24) after second and/or third-line chemotherapy, compared to 8.8 months (range 6-10) for patients with no objective response , or with progressive disease.

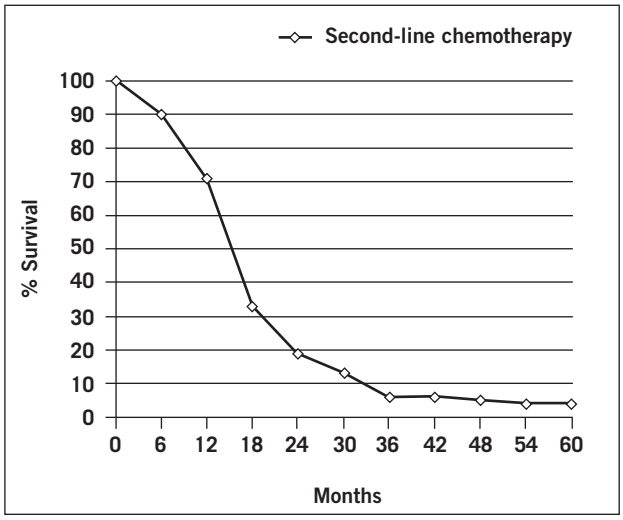

Figure 1 – Estimated overall survival (since admission) of patients that received second-line chemotherapy.

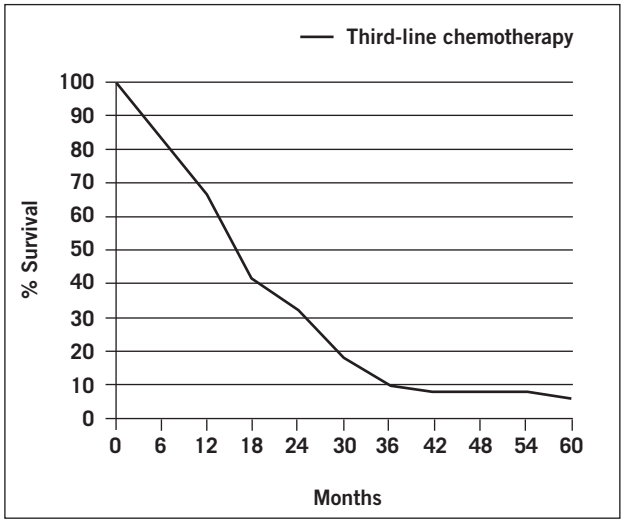

Figure 2 – Estimated overall survival (since admission) of patients that received third-line chemotherapy.

Discussion

The present observational study evaluated survival in patients with advanced NSCLC, related to systemic treatment. This is the largest series of patients with advanced NSCLC studied in our country. Patients included in the study came from two different Brazilian centers specialized in cancer treatment, and probably do not reflect the reality of community approaches in Brazil. Distribution according to gender, age, Karnofsky performance status and histologic type are similar to other studies that included patients with advanced NSCLC[16,17]. In the last two decades, chemotherapy has been established as the standard treatment for advanced NSCLC, in spite of its incurability systemic treatment improve overall survival and quality of life[5,6,9,13]. Since 1990, the availability of third generation drugs (gencitabine, vinorelbine, paclitaxel, docetaxel and irinotecan) as a CDDP-doublet have improved the results of treatment for advanced NSCLC, as shown by Di Maio et al.[18] in a recently published meta-analysis. More recently new options as pemetrexed and molecular-target therapies (bevacizumab, cetuximab, thyrosine-kinase inhibitors) have been added to the therapeutic armamentarium to improve results of treatment for advanced NSCLC[19,20]. As a consequence of the development of multiple new agents with tolerable side effects, the length of chemotherapy for patients with advanced NSCLC has been increasing, with patients receiving chemotherapy beyond first-line drugs, and even maintenance treatment after initial response. The optimal combination of chemotherapy with target agents, second and third-lines chemotherapy, maintenance treatments and the efficacy of new agents remains a challenge. Various characteristics have been used to customize the systemic treatment, such as performance status, histologic subtype, molecular markers and others. However the prognosis remains poor, and one should be able to customize the treatment, selecting patients to different systemic approaches. The efficacy of new chemotherapeutic regimens should be assessed by several clinical endpoints, but overall survival remains as the most important in patients with advanced NSCLC. An increasing number of patients with advanced NSCLC remains in a good performance status after progressing with first line chemotherapy, and should be considered to additional treatments. In the present study we included patients with advanced NSCLC and 58% of them received first line treatment. Almost 24% of our patients received second-line treatment, 8% received third-line and 2.5% received fourth-line of treatment, and this represents a significant number of patients, considering that our series included patients since 1990, and second line chemotherapy has became standard treatment since 2004. Murillo et al.[15] reported different results in a series of patients with advanced NSCLC, 56% received second-line chemotherapy, 26% of patients received third-line, fourth-line chemotherapy was administered to 10% of the patients, and 5% received fifth-line or greater. These results were observed in a community oncology setting in the USA, but different from the present study, the authors included patients from 2000 to 2003, which could explain higher rates of chemotherapy beyond first-line treat-

ment. Based on previous studies[21-24], FDA approved only docetaxel, pemetrexed and erlotinib as options for second line treatment. However different studies have been published with different regimens of second-line chemotherapy, including iriontecan, mytomicin, gencitabine, and even CDDP or carboplatin and other drugs[25,26]. In the present study, we could not analyze the regimens used as second-line treatment due to great heterogeneity of agents. This result is in agreement with our previous study that showed significant heterogeneity of regimens used in the treatment of patients with advanced NSCLC in Brazil[27]. The development of new options to treat patients with advanced NSCLC lead to an increase in the length of treatment, but the prognosis remains poor, with only few patients surviving more than 12 months. However a select group of patients could be eligible to receive prolonged treatment with benefits in terms of survival and palliative care. Identifying prognostic factors is of enormous importance in order to select candidates to prolonged treatment, and avoid futile chemotherapy for poor prognosis patients that will not respond to treatment. Recently, different studies have been shown that wrong selection of patients lead to chemotherapy administered near the end of life, without benefits and probably these treatments have worsened quality of life near the end[26]. Earle et al.[28] in 2004 described results of a Medicare/Surveillance, Epidemiology, and End Results (SEER) database of more than 8,000 chemotherapy treated patients from 1993 to 1996 (53% of lung cancer). The authors observed that 16% of patients received chemotherapy within two weeks before death. More recently, Di Maio et al.[29], reported results of a series of 417 patients with advanced NSCLC treated in community setting. The results disclosed that 43% and 20% of the patients received chemotherapy within two weeks and one month before death, respectively. In the present study, we did not analyze the time of chemotherapy before death, but we have identified prognostic factors in these patients, that could help select patients to receive chemotherapy, even beyond first-line treatment. Our prognostic analysis disclosed that among 2,673 included patients, female gender, higher performance status, histology non-large-cell carcinoma, receive any chemotherapy, objective response to first-line chemotherapy, and receive second-line chemotherapy were determinants of better overall survival. However, at multivariate analysis only performance status, second-line chemotherapy and objective response to first-line chemotherapy were independent determinants of prognosis. Moreover, analysis of patients who received second and/or third-line chemotherapy disclosed that age less than 70 years, and objective response after first-line chemotherapy were determinant of better overall survival. Di Maio et al.[18] analyzed data from nine randomized trials that included patients who received second-line chemotherapy. The authors observed that overall survival was adversely influenced by male gender, poor performance status, histology adenocarcinoma, patients that received platinum, and not obtaining objective response to first-line treatment[2]. Based in their results, a score system was proposed with the aim of identify patients who will obtain better outcomes after second-line chemotherapy. Other prognostic factors have been studied for advanced NSCLC patients, such as molecular markers, that might be important even for select chemotherapeutic agents[30-32]. In our study, we consider only the importance of characteristics that can be evaluated in patients in a community clinical practice. Better overall survival for patients that received second-line chemotherapy suggests that this therapeutic strategy should be considered for a selected group of patients. Based on the present results, performance status and response to first-line chemotherapy could be determinant characteristics to select patients who might be treated beyond first-line chemotherapy. Proper patient selection could increase the range of benefits of second/third line chemotherapy, and avoid futile and costly systemic treatments. Further studies should include also the impact of therapies beyond first-line on quality of life of these patients, treated routinely off protocol.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277-300. Erratum in: CA Cancer J Clin. 2011;61(2):133-4.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90. Erratum in: CA Cancer J Clin. 2011;61(2):134.
3. Brasil. Ministério da Saúde. Instituto Nacional de Câncer. Estimativa 2010: incidência de câncer no Brasil. [cited on 15 May 2011]. Rio de Janeiro: INCA, 2009. Available from: http://www.inca.gov.br/estimativa/2010/.
4. Younes RN, Schutz FA, Gross JL. Preoperative and pathological staging of NSCLC: retrospective analysis of 291 cases. Rev Assoc Med Bras. 2010;56(2):237-41.
5. Ramalingam SS, Dahlberg SE, Langer CJ, Gray R, Belani CP, Brahmer JR, et al. Outcomes for elderly advanced stage non-small cell lung cancer (NSCLC) patients (pts) treated with bevacizumab (B) in combination with carboplatin (C) and paclitaxel (P): analysis of Eastern Cooperative Oncology Group (ECOG) 4599 study. J Clin Oncol 2007;26(1):60-5.
6. Suehisa H, Toyooka S. Adjuvant chemotherapy for completely resected non-small-cell lung cancer. Acta Med Okayama. 2009;63(5):223-30.
7. Temel JS, Greer JA, Admane S, Gallagher ER, Jackson VA, Lynch TJ, et al. Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a Randomized Study of Early Palliative Care. J Clin Oncol. 2011;29(17):2319-26.
8. Sun HB, Wang SY, Ou W, Zhang BB, Yang H, Fang Q. The feasibility of adjuvant carboplatin and docetaxel in patients with curatively resected locally advanced non-small cell lung cancer. Lung Cancer. 2010;68(3):403-8.
9. Tibaldi C, Mazzoni E, Arcabasso G, DIncecco A, Antonuzzo A, Menconi G, et al. Cisplatin plus gemcitabine as adjuvant chemotherapy for radically resected non-small-cell lung cancer: a pilot study. Clin Lung Cancer. 2009;10(1):53-7.
10. Shepherd FA, Abratt R, Crino L, Green M, Sandler A, Steward W, et al. The influence of gemcitabine and cisplatin schedule on response and survival in advanced non-small cell lung cancer. Lung Cancer. 2000;30(2):117-25.

11. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004;22(9):1589-97.
12. Moro-Sibilot D, Vergnenegre A, Smit EF, Toy E, Parente B, Schmitz S, et al. Second-line therapy for NSCLC in clinical practice: baseline results of the European SELECTTION observational study. Curr Med Res Opin. 2010;26(11):2661-72.
13. Owonikoko TK, Ramalingam SS, Belani CP. Maintenance therapy for advanced non-small cell lung cancer: current status, controversies, and emerging consensus. Clin Cancer Res. 2010;16(9):2496-504.
14. Cafarotti S, Leuzzi G, Lococo F, Congedo MT. Mortality, morbidity and late survival in lung resection for non-small cell lung cancer in the elderly population. Interact Cardiovasc Thorac Surg. 2011;12(5):753.
15. Murillo JR Jr, Koeller J. Chemotherapy given near the end of life by community oncologists for advanced non-small cell lung cancer. Oncologist. 2006;11(10):1095-9.
16. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, et al. Cetuximab plus chemotherapyi n patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373(9674):1525-31.
17. Guida C, Maione P, Rossi A, Bareschino M, Schettino C, Barzaghi D, et al. Combined chemo-radiotherapy for locally advanced non-small cell lung cancer: current status and future development. Crit Rev Oncol Hematol. 2008;68(3):222-32.
18. Di Maio M, Chiodini P, Georgoulias V, Hatzidaki D, Takeda K, Wachters FM, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. J Clin Oncol. 2009;27(11):1836-43.
19. Botrel TE, Clark O, Clark L, Paladini L, Faleiros E, Pegoretti B. Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): Systematic review and meta-analysis. Lung Cancer. 2011;74(1):89-97.
20. Ku GY, Haaland BA, de Lima Lopes G Jr. Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: meta-analysis of phase III trials. Lung Cancer. 2011; May 10. [Epub ahead of print]
21. Cohen MH, Johnson JR, Chattopadhyay S, Tang S, Justice R, Sridhara R, et al. Approval summary: erlotinib maintenance therapy of advanced/metastatic non-small cell lung cancer (NSCLC). Oncologist. 2010;15(12):1344-51.
22. De Marinis F, De Santis S, De Petris L. Second-line chemotherapy for non-small cell lung cancer. Ann Oncol. 2006;17(Suppl 5):68-71.
23. Belani CP, Eckardt J. Development of docetaxel in advanced non--small-cell lung cancer. Lung Cancer. 2004;46(Suppl 2):S3-11.
24. Farina G, Longo F, Martelli O, Pavese I, Mancuso A, Moscetti L, et al. Rationale for treatment and study design of TAILOR: a randomized phase III trial of second-line erlotinib versus docetaxel in the treatment of patients affected by advanced non-small-cell lung cancer with the absence of epidermal growth factor receptor mutations. Clin Lung Cancer. 2011;12(2):138-41.
25. Ibrahim EM, Abouelkhair KM, Al-Masri OA, Chaudry NC, Kazkaz GA. Cetuximab-based therapy is effective in chemotherapy-naïve patients with advanced and metastatic non-small-cell lung cancer: a meta-analysis of randomized controlled trials. Lung. 2011;189(3):193-8.
26. Zhang X, Zang J, Xu J, Bai C, Qin Y, Liu K, et al. Maintenance therapy with continuous or switch strategy in advanced non-small-cell lung cancer: a systematic review and meta-analysis. Chest. 2011;140(1):117-26.
27. Naime FF, Younes RN, Kersten BG, Anelli A, Beato CA, Andrade RM, et al. Metastatic non-small cell lung cancer in Brazil: treatment heterogeneity in routine clinical practice. Clinics. 2007;62(4):397-404.
28. Earle CC, Neville BA. Under use of necessary care among cancer survivors. Cancer. 2004;101(8):1712-9.
29. Di Maio M, Lama N, Morabito A, Smit EF, Georgoulias V, Takeda K, et al. Clinical assessment of patients with advanced non-small-cell lung cancer eligible for second-line chemotherapy: a prognostic score from individual data of nine randomised trials. Eur J Cancer. 2010;46(4):735-43.
30. Goldstraw P, Ball D, Jett JR, Le Chevalier T, Lim E, Nicholson AG, et al. Non-small-cell lung cancer. Lancet. 2011 May 10. [Epub ahead of print]
31. Qian Q, Zhan P, Yu L, Shi Y, Cheng J, Wei S, et al. Baseline levels and decrease in serum soluble intercellular adhesion molecule-1 during hemotherapy predict objective response and survival in patients who have advanced non-small-cell lung cancer. Clin Lung Cancer. 2011;12(2):131-7.
32. Donnem T, Andersen S, Al-Saad S, Al-Shibli K, Busund LT, Bremnes RM. Prognostic impact of angiogenic markers in non-small-cell lung cancer is related to tumor size. Clin Lung Cancer. 2011;12(2):106-15.