Adjuvant therapy for non-small cell lung cancer*

Tratamento adjuvante em câncer de pulmão de células não pequenas

Letícia Barbosa França, Márcia Aparecida Oliveira, Isabele Ávila Small, Mauro Zukin, Luiz Henrique de Lima Araújo

Abstract

Objective: Adjuvant chemotherapy is recommended for most patients submitted to resection due to non-small cell lung cancer (NSCLC) staged as II or IIIA. However, although various chemotherapy regimens that include cisplatin have been used in phase III trials, the best choice remains unclear. The objective of this study was to describe the experience of the *Instituto Nacional do Câncer* (INCA, Brazilian National Cancer Institute), located in the city of Rio de Janeiro, Brazil, with the use of the cisplatin-etoposide combination in such patients, with a special focus on survival data. **Methods:** We retrospectively evaluated the medical charts of the patients receiving adjuvant therapy for NSCLC at the INCA between 2004 and 2008. **Results:** We included 51 patients, all of whom were treated with the cisplatin-etoposide combination. The median follow-up period was 31 months, and the median overall survival was 57 months. In the univariate analysis, median survival was lower in the patients submitted to chemotherapy plus radiotherapy than in those submitted to chemotherapy alone (19 vs. 57 months; $p < 0.001$), and there was a trend toward lower median survival in stage III patients than in stage I-II patients (34 vs. 57 months; $p = 0.22$). Overall survival was not significantly associated with gender ($p = 0.70$), histological pattern ($p = 0.33$), or cisplatin dose ($p = 0.13$). **Conclusions:** Our results support the use of adjuvant chemotherapy, and our survival data are similar to those reported in major randomized clinical trials. However, long-term follow-up is warranted in this population.

Keywords: Lung neoplasms; Chemotherapy, adjuvant; Survival analysis.

Resumo

Objetivo: A quimioterapia adjuvante é recomendada na maioria dos casos de câncer de pulmão de células não pequenas (CPCNP) ressecados em pacientes nos estádios II ou IIIA. No entanto, diferentes esquemas quimioterápicos contendo cisplatina foram utilizados em estudos de fase III, e a melhor escolha permanece obscura. O objetivo deste estudo foi descrever a experiência do Instituto Nacional de Câncer (INCA), localizado na cidade do Rio de Janeiro (RJ), com o uso da combinação de cisplatina e etoposídeo nessa situação, com especial foco para os dados de sobrevida. **Métodos:** Foram avaliados retrospectivamente os prontuários dos pacientes com diagnóstico de CPCNP que receberam terapia adjuvante no INCA entre 2004 e 2008. **Resultados:** Foram incluídos 51 pacientes, e todos foram tratados com a combinação de cisplatina e etoposídeo. A mediana de tempo de seguimento foi de 31 meses de seguimento, e a mediana de sobrevida global foi de 57 meses. Na análise univariada, a sobrevida foi inferior nos pacientes submetidos a radioterapia + quimioterapia do que aqueles somente submetidos a quimioterapia (mediana de 19 vs. 57 meses; $p < 0,001$), e houve uma tendência a menor sobrevida nos pacientes em estádio III em relação àqueles em estádios I-II (mediana de 34 vs. 57 meses, respectivamente; $p = 0,22$). Não houve associações significativas entre a sobrevida global e gênero ($p = 0,70$), padrão histológico ($p = 0,33$) ou dose de cisplatina ($p = 0,13$). **Conclusões:** Nossos resultados corroboram a utilização da quimioterapia adjuvante, e os resultados de sobrevida se aproximam daqueles descritos nos principais ensaios clínicos randomizados. Contudo, é importante o acompanhamento a longo prazo nessa população.

Descritores: Neoplasias pulmonares; Quimioterapia adjuvante; Análise de sobrevida.

---

* Study carried out at the *Instituto Nacional do Câncer* – INCA, Brazilian National Cancer Institute – Rio de Janeiro, Brazil.
Correspondence to: Letícia Barbosa França. Rua Marechal Floriano Peixoto, 1600, Edifício Vilagio Piemonte, apto. 1202, Duque de Caxias, CEP 78043-395, Cuiabá, MT, Brasil.
Tel. 55 21 8348-6315. E-mail: lb-franca@uol.com.br
Financial support: None.
Submitted: 16 December 2010. Accepted, after review: 28 March 2011.

Introduction

Lung cancer is the leading cause of cancer death in men and women worldwide, accounting for approximately 1.2 million deaths per year.[1] Although the mortality rate has declined among men, it continues to increase among women, accounting for approximately half of all deaths from lung cancer worldwide.[2] In Brazil, the estimated numbers of new cases for 2010 are 17,800 in men and 9,830 in women, corresponding to an estimated incidence of 18 new cases per 100,000 men and 10 new cases per 100,000 women.[3]

Lung cancer includes various histological types, such as small cell lung cancer and the different types of non-small cell lung cancer (NSCLC). The latter subtype, which includes squamous cell carcinoma, adenocarcinoma (including noninvasive bronchioloalveolar carcinoma), and large cell carcinoma, accounts for approximately 80% of cases.[4,5] The major risk factor is smoking, which is involved in approximately 85% of cases.

The treatment of NSCLC depends on the histological type and on the initial disease stage, as well as on the clinical status of the patient. Surgery is the predominant therapy for clinical stages I through IIIA. However, even patients submitted to complete surgical resection with curative intent have a recurrence rate of 50%, most of which is distant recurrence.[6,7] In this context, adjuvant therapy has been shown to play an important role, resulting in an improvement in survival, as has been confirmed in phase III trials.

The incorporation of adjuvant therapy on a global scale has direct implications for the routine of health care facilities, as well as for health care costs. Therefore, a better understanding of the outcomes seen in Brazil is essential for mapping the local characteristics, making it possible to establish priorities for resource allocation in oncology. At the *Instituto Nacional do Câncer* (INCA, Brazilian National Cancer Institute), adjuvant chemotherapy has long been the standard treatment for patients undergoing tumor resection, and the cisplatin-etoposide combination has been used in such patients since 2004, after the dissemination of the initial results of a study on the topic.[8] The objective of the present study was to describe the overall survival of such patients and to compare that with the findings of studies published to date.

Methods

This was a retrospective descriptive study. A list of patients was obtained from the records of the Hospital Information System of INCA Unit I. The medical charts of those patients were reviewed for the collection of information, which was recorded on a standard form. Data collection was performed at INCA Unit I. Among the baseline characteristics assessed were age, performance status, smoking, comorbidities, initial disease stage, date of diagnosis, and current disease status. Regarding adjuvant therapy, the number of courses used was assessed, as were the dates of the courses, the date of recurrence after treatment, and the date of death or the date of the last visit to the facility. The data on the forms were entered into an electronic spreadsheet (Microsoft Excel 97) for subsequent analysis. The study was approved by the INCA Research Ethics Committee.

We included patients with NSCLC undergoing primary surgical resection with curative intent and receiving adjuvant chemotherapy based on cisplatin at the INCA between January of 2004 and December of 2008. The exclusion criteria were as follows: having a concomitant malignant neoplasm; having previously undergone chemotherapy; and having macroscopic residual disease after surgical treatment.

Adjuvant chemotherapy was initiated within 60 days after surgery and consisted of a combination of cisplatin (a 2-h i.v. infusion of 80 mg/m^2 on day 1) and etoposide (a 1-h i.v. infusion of 300 mg/m^2, divided between days 1 and 3). The patients received up to 4 courses of the combination, unless there was toxicity or the occurrence of limiting complications. Some patients received adjuvant radiotherapy after completion of chemotherapy, especially when neoplastic involvement of mediastinal lymph nodes was detected during surgery. The dose used on the tumor bed and the mediastinum was 60 Gy, with conventional fractionation of daily applications on weekdays.

The statistical analyses were performed with the Statistical Package for the Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, USA). Overall survival and disease-free survival were determined by Kaplan-Meier curves, whereas

the log-rank test was used for the analysis of the variables. Overall survival was defined as the time interval between the first day of the first course of adjuvant chemotherapy and the date of death or the date of the last visit to the hospital (emergency room or outpatient visit). Disease-free survival was defined as the time interval between the initiation of adjuvant chemotherapy and the documentation of recurrence, death, or discontinuation of follow-up.

Results

We included 51 patients. The median age was 61 years (range, 40-76 years). Of those 51 patients, 27 (53%) were female and 24 (47%) were male. Forty-six patients (90%) were smokers or former smokers. The most common histological type was adenocarcinoma (in 57% of the cases), followed by squamous cell carcinoma (in 33%). In 40%, 32%, and 27% of the patients, respectively, the disease was in stage I, II, or III. Lobectomy was the predominant surgical procedure employed, being performed in 40 patients (80%). Only 7 patients (14%) underwent pneumonectomy, whereas 4 (6%) underwent bilobectomy. Adjuvant chemotherapy consisted of cisplatin plus etoposide in all cases, with a median of 4 courses (range: 1-4). Although the initial cisplatin dose was 80 mg/m^2 in 30 patients (59%), 41 (80%) received at least 75 mg/m^2 as the initial dose. Thirty-nine patients (76%) received an initial etoposide dose of 300 mg/m^2, and 11 patients (22%), of whom 5 had stage I or II disease and 6 had stage III disease, also received adjuvant radiotherapy after chemotherapy. The baseline characteristics are summarized in Table 1.

The median follow-up period was 31 months (95% CI: 28.4-34.1), and the median overall survival was 57 months (95% CI: 40.4-73.5; Figure 1). The proportion of patients surviving at 12, 36, and 60 months, respectively, was 95%, 70%, and 31%. As shown in Figure 2, there was a trend toward lower median survival in stage III patients than in stage I/II patients (34 months; 95% CI: 18.2-51.4 vs. 57 months; 95% CI: 40.4-73.5; p = 0.22). Median survival was 19 months in the patients who received adjuvant radiotherapy, compared with 57 months in those who did not (p < 0.001). There were no differences in overall survival in terms of gender (p = 0.70), histological pattern (p = 0.33), or cisplatin dose (p = 0.13).

Table 1 - Baseline characteristics of the 51 patients included in the study.[a]

Characteristic	Value
Age, years[b]	61
Gender	
Male	47
Female	53
Performance status	
0	26
1	74
2	0
Histological pattern	
Adenocarcinoma	57
SCC	33
Other	10
Stage	
I	40
II	33
III	27
Treatment	
C+E	100
C+VR	0
C+VB	0
Type of resection	
Lobectomy	80
Bilobectomy	6
Pneumonectomy	14
Adjuvant radiotherapy	22

SCC: squamous cell carcinoma; C: cisplatin; E: etoposide; VR: vinorelbine; and VB: vinblastine. [a]Values expressed as %, except where otherwise indicated. [b]Value expressed as median.

Discussion

The results of the present study are in accordance with those reported in the first published randomized clinical trials of adjuvant chemotherapy for NSCLC. The median overall survival found in the present study (57 months), in particular, is similar to that described in another study (54 months).[8] In fact, some baseline characteristics, such as age, histological type, and distribution by stage, were similar between the patients treated at the INCA and the cohort of patients of that study.

A distinguishing characteristic of the present study was the use of the cisplatin-etoposide combination in all patients. Etoposide is a

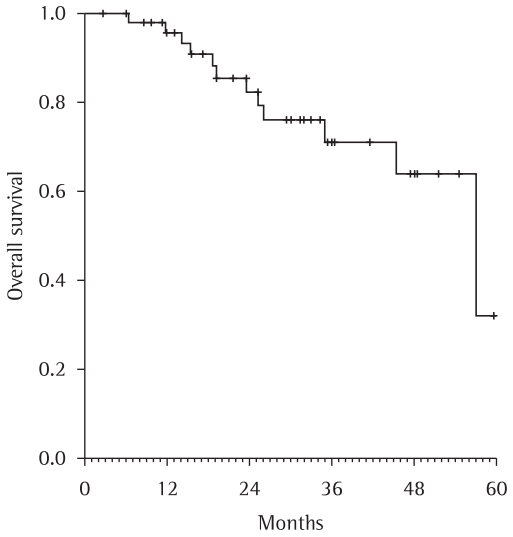

Figure 1 - Kaplan-Meier survival curve for overall survival in the sample as a whole.

cytotoxic agent of the epipodophyllotoxin class.[9] Its antitumor activity results from its ability to interact with and inhibit the activity of the topoisomerase II enzyme, which leads to an accumulation of DNA cleavage complexes and subsequent cell death. Etoposide is one of the first-generation platinum compounds employed in advanced NSCLC, compounds that have largely been supplanted by new agents, especially in developed countries.[10]

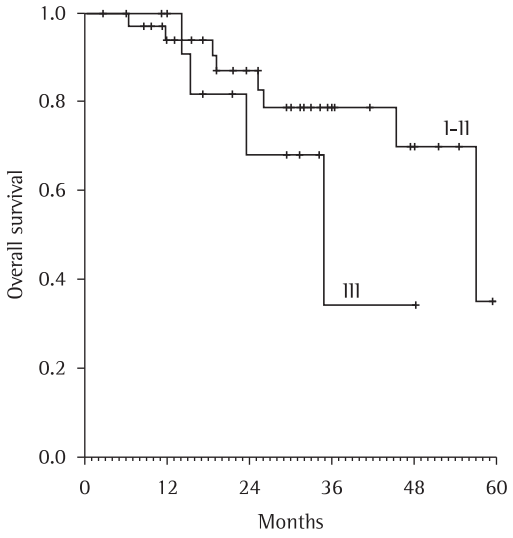

Figure 2 - Kaplan-Meier survival curves for overall survival in stage I/II patients (median = 34 months) and stage III patients (median = 57 months; p = 0.22).

In initial NSCLC, the cisplatin-etoposide combination was used in 57% of the patients in the study conducted by Arriagada et al.[8] The early results of that study support the use of the cisplatin-etoposide combination,[8] because the patients receiving that combination had better survival than did those randomized to observation. However, the results of a study conducted more recently by the same group of authors[11] revealed an increase in the mortality rate after a five-year median follow-up period. Therefore, the initial improvement in survival lost statistical power, with a benefit of 3.9% (p = 0.10). Conversely, in two other studies, the combination of cisplatin and the vinca alkaloid vinorelbine was used.[12,13] Unlike the study conducted by Arriagada et al,[11] those two other studies produced promising results: an improvement in survival was confirmed after a long follow-up period. In another study,[14] this improvement was 11% after more than nine years of follow-up, which is in disagreement with the findings of the Arriagada et al. study.[11] In addition, in a recent meta-analysis,[15] extremely positive results were obtained with the cisplatin-vinorelbine combination, with a reduction in the overall mortality rate of 8.9% in comparison with observation (hazard ratio [HR] = 0.80; 95% CI: 0.70-0.91; p < 0.001). That analysis used data from four clinical trials, collectively involving 1,888 patients. In fact, those results are more consistent than are the results of other meta-analyses compared in the same study,[15] which allowed the use of other chemotherapy regimens (HR = 0.95; 95% CI: 0.86-1.05; interaction test = 0.04). The median survival described in the present study, as well as that described in the Arriagada et al. study,[8] is clearly lower than the median survival of 94 months described in the study conducted by Winton et al.[12] However, caution is required when comparing these results, because differences in patient selection are likely to have influenced this evaluation. Of note is the fact that only stage I or II patients were included in the Winton et al. study,[12] such patients being known to have a better prognosis, regardless of the treatment.

In the present study, a significant proportion of stage I patients (40%) received adjuvant therapy. As previously mentioned, the use of adjuvant chemotherapy in such patients is highly controversial. A subgroup analysis of

major clinical trials and meta-analyses failed to demonstrate any benefit of the treatment. In one meta-analysis,[15] the absolute improvement, although not statistically significant, was 1.8% in such a subgroup (HR = 1.0; 95% CI: 0.78-1.30). Apparently, patients with tumors larger than 4 cm can benefit from adjuvant therapy, as has been observed in subgroup analyses of two studies.[12,16] In the present study, stage I patients had better survival, which reflects their better prognosis. However, it is not possible to draw conclusions about the effects of chemotherapy on this subgroup on the basis of our data, because our study did not have a control arm.

In the cohort described here, median survival was lower in the patients receiving adjuvant radiotherapy ($p < 0.001$). These data are in accordance with the results of a meta-analysis of 2,232 patients,[17] in which postoperative radiotherapy was found to have a deleterious effect on the survival of patients with N0 or N1 disease, despite possibly being beneficial to those with N2 disease (stage III). In fact, approximately half of the patients receiving radiotherapy at the INCA between 2004 and 2008 had stage I or II disease. However, the present study does not allow inferences about the potential negative effects of radiotherapy in this group of patients. Therefore, this issue has yet to be clarified in studies appropriately designed for this purpose.

In summary, our results support the use of adjuvant chemotherapy, and our survival data are similar to those reported in major randomized clinical trials. However, long-term follow-up is warranted in this population, because the results obtained with combinations of next-generation drugs, especially cisplatin and vinorelbine, have been shown to be more consistent after the first five years of follow-up.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, 2008. CA Cancer J Clin. 2008;58(2):71-96.
3. Instituto Nacional de Câncer – INCA [homepage on the Internet]. Brasília: Ministério da Saude [cited 2010 Sep 25]. Estimativa 2010: incidência de câncer no Brasil. [Adobe Acrobat document, 100p.]. Available from: http://www1.inca.gov.br/estimativa/2010/estimativa20091201.pdf
4. Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new World Health Organization classification of lung tumours. Eur Respir J. 2001;18(6):1059-68.
5. Gazdar AF. Should we continue to use the term non-small-cell lung cancer? Ann Oncol. 2010;21 Suppl 7:vii225-vii229.
6. Feld R, Rubinstein LV, Weisenberger TH. Sites of recurrence in resected stage I non-small-cell lung cancer: a guide for future studies. J Clin Oncol. 1984;2(12):1352-8.
7. Immerman SC, Vanecko RM, Fry WA, Head LR, Shields TW. Site of recurrence in patients with stages I and II carcinoma of the lung resected for cure. Ann Thorac Surg. 1981;32(1):23-7.
8. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004;350(4):351-60.
9. Takimoto CH. Topoisomerase interactive agents. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer Principles and Practice of Oncology. Philadelphia: Lippincott, Williams & Wilkins; 2005. p. 381-4.
10. Bonomi P, Kim K, Chang A, Johnson D. Phase III Trial comparing etoposide (E), cisplatin (C), versus taxol (T) with cisplatin-G-CSF (G), versus taxol-cisplatin in advanced non-small cell lung cancer. An Eastern Cooperative Oncology Group (ECOG) trial. Proc Am Soc Clin Oncol. 1996;15:382a.
11. Arriagada R, Dunant A, Pignon JP, Bergman B, Chabowski M, Grunenwald D, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol. 2010;28(1):35-42.
12. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2005;352(25):2589-97.
13. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzáles-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7(9):719-27.
14. Butts CA, Ding K, Seymour L, Twumasi-Ankrah P, Graham B, Gandara D, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. J Clin Oncol. 2010;28(1):29-34.
15. Douillard JY, Tribodet H, Aubert D, Shepherd FA, Rosell R, Ding K, et al. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol. 2010;5(2):220-8.
16. Strauss GM, Herndon JE 2nd, Maddaus MA, Johnstone DW, Johnson EA, Harpole DH, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol. 2008;26(31):5043-51.
17. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. Lancet. 1998;352(9124):257-63.

About the authors

Letícia Barbosa França
Physician. Department of Clinical Oncology, *Instituto Nacional do Câncer* – INCA, Brazilian National Cancer Institute – Rio de Janeiro, Brazil.

Márcia Aparecida Oliveira
Physician. Department of Clinical Oncology, *Instituto Nacional do Câncer* – INCA, Brazilian National Cancer Institute – Rio de Janeiro, Brazil.

Isabele Ávila Small
Coordinator for Clinical Research and Incorporation of New Technologies. *Instituto Nacional do Câncer* – INCA, Brazilian National Cancer Institute – Rio de Janeiro, Brazil.

Mauro Zukin
Physician. Department of Clinical Oncology, *Instituto Nacional do Câncer* – INCA, Brazilian National Cancer Institute – Rio de Janeiro, Brazil.

Luiz Henrique de Lima Araújo
Coordinator for Clinical Research and Incorporation of New Technologies. *Instituto Nacional do Câncer* – INCA, Brazilian National Cancer Institute – Rio de Janeiro, Brazil.