CISPLATIN-BASED CHEMOTHERAPY IN ELDERLY PATIENTS WITH NON-SMALL CELL LUNG CANCER

Jian Li1*, Xiao-Qin Li2, Young-Jie Du1, Li-Ping Ge1, Chun-Hua Dai2, Ping Chen1

Departments of 1Pulmonary Medicine and 2Medical Oncology, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu, China.

SUMMARY

Background: The use of cisplatin-based combination chemotherapy in elderly patients with advanced non-small cell lung cancer (NSCLC) remains an issue of debate.

Methods: We retrospectively reviewed the medical records of all patients ≥70 years with stage IIIB and stage IV NSCLC who received chemotherapy between 2000 and 2007 at our hospital. Data on demographic information, chemotherapy regimen and cycle, response, toxicity, and survival time were collected. Survival was analyzed by the Kaplan-Meier method and log-rank test.

Results: A total of 102 elderly patients with advanced NSCLC received chemotherapy with a combination of cisplatin plus either vinorelbine or gemcitabine (the cisplatin-based combination group), or single-agent vinorelbine or gemcitabine (the single-agent group). The response rate was 46% in the cisplatin-based combination group, and 25% in the single-agent group (p = 0.03). The median survival was 11.1 months (95% confidence interval, CI, 9.24–12.96) in the cisplatin-based combination group, and 8.9 months (95% CI, 7.68–10.14) in the single-agent group (p = 0.06), and 1-year survival rates were 38.6% and 22.4%, respectively. The median progression-free survival was 7.9 months (95% CI, 5.62–10.18) and 5.8 months (95% CI, 4.78–6.82), respectively (p = 0.03). Grade 3–4 anemia and neutropenia were more frequent in the cisplatin-based combination group. Other toxicities were mild and generally well tolerated in the two groups.

Conclusion: Elderly patients ≥70 years with advanced NSCLC can tolerate and benefit from cisplatin-based combination chemotherapy. Cisplatin-based chemotherapy may be considered as an option in the treatment of elderly patients with advanced NSCLC. [International Journal of Gerontology 2010; 4(1): 28–36]

Key Words: advanced, chemotherapy, cisplatin, elderly, non-small cell lung cancer

Introduction

Lung cancer is the most common malignancy in the world and the leading cause of tumor-related death in developed countries1. Approximately 80–85% of lung cancer subtypes are of non-small cell histology. Non-small cell lung cancer (NSCLC) is also one of the most common malignant tumors in China. It is usually locally advanced or advanced in presentation and is rarely diagnosed at an early stage. Although the median age of patients with newly diagnosed NSCLC participating in clinical trials is 60–62 years, more than 50% of cases of advanced NSCLC are diagnosed in patients ≥65 years, and approximately 30–40% of cases are diagnosed in patients ≥70 years2–3. Evidence from earlier clinical trials confirms that platinum-based chemotherapy regimens can increase overall survival and improve the quality of life compared with best supportive care in patients with advanced NSCLC4. Therefore, platinum-based combination chemotherapy has become the standard treatment for patients aged <70 years with advanced NSCLC5. Because of the risks associated with its potential toxicity, however, chemotherapy is often
Chemotherapy in NSCLC Elderly Patients

withheld from elderly patients. The elderly typically have a greater number of non-cancer comorbidities and poorer performance status (PS) at diagnosis than younger patients with the same extent of disease. Moreover, age-related physiologic changes in functional status, organ function, and pharmacokinetics make the selection of their optimal treatment more challenging.

Although a consensus is emerging that elderly patients can benefit from chemotherapy, it is less clear whether single-agent or combination therapy is preferable, or whether particular agents have advantages for initial treatment. Several clinical trials with single-agent therapy of vinorelbine or gemcitabine have shown good activity and tolerability for elderly patients with advanced NSCLC. However, the role of platinum-based combination chemotherapy in elderly patients remains controversial. To date, prospective phase III trials with platinum-based chemotherapy for elderly patients are still lacking. Evidence to support the use of a platinum-based combination regimen in elderly patients with advanced NSCLC comes only from retrospective analyses of the subset of large randomized trials using platinum-based chemotherapy, which suggested that main treatment outcome did not differ between elderly patients and younger patients. While awaiting further results from ongoing clinical trials specifically designed for elderly patients, evidence from retrospective study can be helpful. During the past decade, a number of patients ≥70 years with unresectable, locally advanced and metastatic NSCLC received chemotherapy at our hospital. In the present study, we reviewed our experience between 2000 and 2007, with elderly patients treated with chemotherapy for stage IIIB and IV NSCLC, and compared the efficacy and toxicity of cisplatin-based combination regimens (cisplatin plus vinorelbine or cisplatin plus gemcitabine) with single-agent regimens (vinorelbine or gemcitabine) in these patient populations.

Subjects and Methods

Clinical information was obtained through a detailed retrospective review of the medical records of all elderly patients who received chemotherapy for stage IIIB and IV NSCLC at the Affiliated Hospital of Jiangsu University in China from January 2000 to June 2007. We limited our analyses only to patients ≥70 years who had been diagnosed with unresectable, locally advanced and metastatic NSCLC, and who received combination chemotherapy with cisplatin plus either vinorelbine or gemcitabine, or single-agent chemotherapy with vinorelbine or gemcitabine as first-line therapy.

The data recorded included demographic information, staging procedure, pretherapy clinical assessment, and comorbidity number. All patients were staged on the basis of medical history, physical examination, chest radiography, fiberoptic bronchoscopy, brain and chest computed tomography scan, abdominal ultrasound or abdominal computed tomography scan, and radionuclide scan of bone. All patients had histologically or cytologically proven stage IIIB (with malignant effusion or metastatic supraclavicular lymph nodes) or IV NSCLC, and had an Eastern Cooperative Oncology Group PS of ≤2, and had radiographically measurable or assessable disease and adequate hematologic, renal and hepatic function. Patients with brain metastases or who previously were treated with a biologic response modifier, or those with a history of other malignant tumors were excluded from this study. Patients who had undergone radiotherapy were included in this analysis provided that chest radiotherapy was performed in patients with stage IIIB disease without pleural effusion who had an objective response or stable disease after the completion of three to four cycles of chemotherapy, or who had progressive disease at any time provided that distant metastases had not appeared. Data on the chemotherapy regimen, number of cycles, toxicity, objective response, and date of disease progression and death were collected. Survival data were last collected in April 2008.

Comorbidities mainly included arrhythmias, hypertension, ischemia cardiopathy, cerebral vascular disease, chronic obstructive pulmonary disease, mild liver disease, peptic ulcer, benign prostatic hypertrophy, and diabetes. Diagnosis of a comorbidity was made according to the international criteria of these diseases, based on relevant examination, such as electrocardiogram, blood pressure measurement, coronary arteriography, and brain computed tomography scan or angiography.

Chest radiography was performed before each cycle, and computed tomography scans were performed every two or three cycles to evaluate the response to treatment. Brain computed tomography and bone scan were repeated only if clinically indicated. Tumor response was assessed according to World Health Organization criteria. A complete response was defined as the complete disappearance of all clinically detectable tumors.
for at least 4 weeks. A partial response was defined as a reduction of ≥50% in the product of the largest perpendicular diameters of one or more measurable lesions lasting for 4 weeks with no new areas of malignant disease. Stable disease was defined as a <50% reduction or a <25% increase in all measurable lesions with the appearance of no new lesions. Progressive disease was defined as a 25% increase in the product of two perpendicular diameters of any measured lesion or the development of new lesion. The best response was recorded for each patient. Toxicity for each cycle was assessed using the World Health Organization criteria before the beginning of the next cycle, and hematologic toxicity assessment was performed weekly. The worst data for each patient in all cycles of chemotherapy were used in the toxicity analysis.

Outcomes were determined from multiple sources including the medical records, referring physicians, and patients’ families. Overall survival was calculated from the date of the first cycle of chemotherapy to the date of death from any cause or the last follow-up visit. Progression-free survival was calculated from the date of the first cycle of chemotherapy to the date of disease progression, recurrence, or death from any causes. Survival curves were estimated using the Kaplan-Meier method. The comparisons of survival time between patients with different characteristics were performed by the log-rank test. The χ² test or the Fisher exact test was used in the response rate comparison and the toxicity analysis. Statistical significance was defined as p < 0.05.

Results

Treatment regimen

From January 2000 to June 2007, 146 patients 70 years and older with stage IIIB or IV NSCLC received chemotherapy with combination or single-agent regimens. Of these, 102 patients were eligible and assessable. The reason for ineligibility included Eastern Cooperative Oncology Group PS > 2 (n = 9), brain metastasis (n = 8), loss to follow-up (n = 6), previous malignant disease (n = 2), and other chemotherapy regimens including cisplatin plus etoposide (n = 7), vinorelbine plus gemcitabine (n = 6), cisplatin plus paclitaxel (n = 4), and docetaxel (n = 2). Characteristics of the 102 patients included in the present study are listed in Table 1. These 102 patients were divided into two groups according to chemotherapy regimens: (1) cisplatin-based combination group, including the patients treated with cisplatin plus vinorelbine (cisplatin 60–70 mg/m² on day 1 and vinorelbine 20–25 mg/m² on days 1 and 8 every 3 weeks) (n = 29) and those with cisplatin plus gemcitabine (cisplatin 60–70 mg/m² on day 1 and gemcitabine 800–1,000 mg/m² on days 1 and 8 every 3 weeks) (n = 25); and (2) single-agent group, including the patients treated with vinorelbine (vinorelbine 25–30 mg/m² on days 1, 8 and 15 every 4 weeks) (n = 26) and those with gemcitabine (gemcitabine 1,000–1,200 mg/m² on days 1, 8 and 15 every 4 weeks) (n = 22). The doses and regimen of chemotherapy were used at the discretion of each treating physician based on patient PS and toxicity. Changes in dosage were based on hematologic test results obtained on day 1 of chemotherapy; if neutrophils were <1.5 × 10⁹/L, and platelets were <100 × 10⁹/L, treatment was delayed by 1 week. Treatment on day 8 had to be cancelled if neutrophil counts were <1.0 × 10⁹/L and platelets were <100 × 10⁹/L. All patients received an antiemetic prophylaxis that consisted of 5-hydroxytryptamine type 3 receptor antagonists and dexamethasone, and patients treated with cisplatin-based combination received adequate hydration. Patients were treated for a maximum of six cycles or until intolerable toxicity, progressive disease, or death.

The two groups were well balanced with respect to the main characteristics (Table 1). Approximately 75% of the patients were males, and approximately 65% of the patients had an Eastern Cooperative Oncology Group PS of 0 or 1. One-third of the patients presented with stage IIIB disease. In each group, the predominant histology was squamous-cell carcinoma, and more patients had metastatic sites of one or two. There were slightly more patients with one or no comorbidity in the cisplatin-based combination group than in the single-agent group.

Treatment response

The median number of chemotherapy cycles received was three (range, 1–6) for the cisplatin-based combination group, and four (range, 1–6) for the single-agent group. The mean dose intensities were 17.8 mg/m²/week (range, 13.9–22.1 mg/m²/week) and 13.2 mg/m²/week (range, 11.6–15.1 mg/m²/week) for cisplatin and vinorelbine, respectively, for combined treatment, and 18.4 mg/m²/week (range, 13.6–22.7 mg/m²/week) and 526 mg/m²/week (range, 480–576 mg/m²/week) for cisplatin and gemcitabine, respectively, for combined treatment. In the single-agent group, the mean dose
intensities of vinorelbine and gemcitabine were 18.1 mg/m²/week (range, 14.2–21.8 mg/m²/week) and 745 mg/m²/week (range, 704–789 mg/m²/week), respectively.

Treatment results and objective response are shown in Table 2. Objective response could not be evaluated in 10 patients because of discontinuation before cycle 2 for the following reasons: toxicity (n=3), patient refusal (n=2), early death (n=1), and unconfirmed response after the completion of two cycles (n=4). The overall response rate (complete response and partial response) for the cisplatin-based combination group was 46%, whereas it was 25% for the single-agent group (p=0.03).

After the end of first-line chemotherapy, 38 patients (37%) received second-line therapy because of a lack of response to first-line therapy, or recurrence or progression of the disease. Forty-eight percent of patients initially treated with single-agent chemotherapy received second-line therapy compared with 28% for patients initially treated with cisplatin-based combination (p=0.04). Furthermore, 30% of patients in the single-agent group received a cisplatin-based combination as second-line therapy compared with 9% of patients in the cisplatin-based combination group (p=0.01). Sixteen patients (17%) received second-line gefitinib (Table 2). Nine patients with stage IIIIB and supraclavicular lymph nodes metastases underwent chest radiotherapy after the completion of three to four cycles of chemotherapy, five were in the cisplatin-based combination group, and four were in the single-agent group.

Toxicity
The most relevant toxic events are summarized in Table 3. The incidences of grade 3 and 4 anemia and neutropenia were significantly higher in the cisplatin-based combination group than in the single-agent group.
group ($p = 0.04$ and $p = 0.02$, respectively). However, the incidence of neutropenia fever was similar between both arms. There was not a significant difference in the occurrence of thrombocytopenia and nonhematologic toxicity between two groups, although nausea and emesis were more common in the cisplatin-based combination group.

**Survival**

The median survival time for the entire study population was 9.5 months (95% confidence interval, CI, 7.68–11.42), and the 1- and 2-year survival rates were 31.4% and 7%, respectively. The median progression-free survival of all patients was 6.5 months (95% CI, 5.28–7.72), and the 1-year progression-free survival rate was 10.5%. The median survival time was 11.1 months (95% CI, 9.24–12.96) in the cisplatin-based combination group compared with 8.9 months (95% CI, 7.68–10.14) in the single-agent group. The 1- and 2-year survival rates were 38.6% and 9.1%, respectively, in the combination group compared with 22.4% and 4.8%, respectively, in the single-agent group (Figure 1). Although there was no statistically significant difference in overall survival time between two groups, cisplatin-based chemotherapy showed a trend toward improved overall survival ($p = 0.06$). For the cisplatin-based combination group,
the median progression-free survival was 7.9 months (95% CI, 5.62–10.18), compared with 5.8 months (95% CI, 4.78–6.82) for the single-agent group (Figure 2). A significant difference in median progression-free survival between two groups was observed ($p = 0.03$).

The overall survival of patients in the two groups according to the PS and comorbidity are summarized in Table 4. Patients with a PS of 2 or ≥2 comorbidities had a significantly worse outcome compared with patients with PS of 0 to 1 or with 1 or no comorbidity. In the cisplatin-based combination group, median survival and 1-year survival rates were 11.6 months and 39.4%, respectively, for patients with PS of 0 to 1, and 9.0 months and 22.8%, respectively, for patients with PS of 2 ($p = 0.04$). In the single-agent group, median survival and 1-year survival rates were 9.8 months and 29.8%, respectively, for patients with PS of 0 to 1, and 7.5 months and 17.5%, respectively, for patients with PS of 2 ($p = 0.06$). Median survival was 11.8 months for patients with 1 or no comorbidity, 8.6 months for patients with ≥2 comorbidities in the cisplatin-based combination group ($p = 0.04$), and 9.5 months and 7.1 months for patients with 1 or no comorbidity and patients with ≥2 comorbidities in the single-agent group, respectively ($p = 0.046$).

**Discussion**

Newer chemotherapy regimens with third-generation cytotoxic agents in combination with cisplatin have been shown to be better tolerated than older cisplatin-based regimens, and some randomized trials have also shown greater efficacy and survival benefits with these newer combinations for the treatment of advanced NSCLC\textsuperscript{14–16}. However, because of the potential
toxicities of cisplatin-based chemotherapy regimens and the modest survival benefit, this treatment is not offered to many elderly patients or patients with poor PS. To date, the optimal regimen for elderly patients with advanced NSCLC is still a controversial issue.

In the third-generation cytotoxic agents, a single-agent chemotherapy regimen of vinorelbine or gemcitabine has been investigated widely in elderly patients with advanced NSCLC. In phase II trials specifically designed for elderly patients with advanced NSCLC, vinorelbine yielded overall response rates of 12–23% and median survival times of 8.3–10 months, and gemcitabine yielded an objective response rate of 22–33% and median survival times of 7.4–9 months. Vinorelbine plus gemcitabine is the most common non-platinum chemotherapy combination used in elderly patients. Phase II trials of vinorelbine plus gemcitabine in elderly patients with NSCLC have shown response rates between 18% and 65%, and a median survival time range from 10 to 11 months. These regimens were generally well tolerated. However, there is continued controversy over the relative merits of combination versus single-agent therapy in elderly patients. Randomized phase III trials from Italy with patients ≥70 years showed conflicting survival findings. In one of these trials, the investigators found no difference in response rates or survival times for elderly patients with advanced NSCLC who received combination chemotherapy with vinorelbine plus gemcitabine compared with vinorelbine alone or gemcitabine alone. Quality of life was similar for the combination versus single-agent group. However, toxicity was greater for patients who received combination chemotherapy compared with vinorelbine alone or gemcitabine alone. Quality of life was similar for the combination versus single-agent group; however, toxicity was greater for patients who received combination chemotherapy.

Another study showed that vinorelbine and gemcitabine combination therapy was associated with significantly better response rate and survival in elderly patients with advanced NSCLC than vinorelbine alone. Combination therapy was also associated with a clear delay in symptom progression and deterioration in quality of life. Based on the conflicting results of these phase III trials, the benefit of single-agent versus combination chemotherapy in elderly patients is an area that needs additional study.

In our retrospective study, we evaluated the efficacy of cisplatin-based combination regimen compared with single-agent regimen (vinorelbine or gemcitabine) in terms of response rate, toxicity and survival in elderly patients with stage IIIB and IV NSCLC. Results showed that the overall response rate and progression-free survival of patients treated with cisplatin-based combination regimen were substantially better than those with single-agent therapy. Although there was no statistically significant difference in overall survival between two groups, cisplatin-based combination chemotherapy showed a trend toward improved overall survival (p = 0.06). One possible explanation for this result is the impact of second-line therapy, which has shown to improve survival compared with no therapy or ineffective therapy. In the present study, the rate of second-line therapy in the single-agent group was significantly higher compared with the cisplatin-based combination group (p = 0.04). Moreover, the rate of patients initially treated with a single-agent received a cisplatin-based combination as second-line therapy was markedly higher than those initially treated with a cisplatin-based combination (p = 0.01). Another explanation may be related to the bias of retrospective study. Although the incidences of grade 3–4 anemia and neutropenia were higher in patients treated with the cisplatin-based combination regimen than those with the single-agent regimen, other toxicities were mild and generally well tolerated in two groups.

A phase III randomized trial conducted by Scagliotti et al. has demonstrated that there were no significant differences in objective response, overall survival, time to disease progression, and quality of life between patients treated with cisplatin plus vinorelbine and patients treated with cisplatin plus gemcitabine for advanced NSCLC. For the purpose of analyses, therefore, patients treated with cisplatin plus vinorelbine and those with cisplatin plus gemcitabine were grouped together as the cisplatin-based combination group, and patients treated with vinorelbine and those with gemcitabine were considered as the single-agent group in this study.

The role of platinum-based combination chemotherapy in elderly patients with advanced NSCLC remains to be clarified. A retrospective analysis of cisplatin-based chemotherapy in NSCLC patients revealed a significant increase in death within 30 days of starting chemotherapy with increasing age. It is possible that a reduction of renal, hepatic and bone-marrow function in elderly patients increases the potential for toxicity. However, some retrospective analyses of elderly patient subgroups from randomized studies support the use of platinum-based regimens in advanced NSCLC patients ≥70 years. These analyses showed a similar outcome of platinum-based chemotherapy for elderly patients compared with their younger counterparts.
in terms of response rate and overall survival, with a similar toxicity and no significant adverse effects on quality of life\textsuperscript{11–13}. In addition, phase II trials of the combination of third-generation cytotoxic agents with cisplatin in modified schedules or attenuated doses have been demonstrated to be an active and well-tolerated treatment in elderly patients\textsuperscript{27,28}. In the present study, patients treated with cisplatin-based combination regimen also received attenuated doses of chemotherapy.

Although our data should be interpreted with caution because the results came from a retrospective study and a relatively small number of patients were analyzed, we conclude that it is possible that cisplatin-based combination substantially improves the prognosis of elderly patients with advanced NSCLC compared with single-agent vinorelbine or gemcitabine chemotherapy. The improvement obtained with cisplatin-based combination chemotherapy can be explained by the higher response rates and a longer overall survival and progression-free survival than single-agent chemotherapy, along with an acceptable toxicity. In addition, patients with good PS and fewer comorbidities had improved overall survival, regardless of chemotherapy regimen. Therefore, PS and comorbidities should not be ignored in the selection of elderly patient treatment.

In summary, our results show that selected elderly patients \( \geq 70 \) years with advanced NSCLC may tolerate and benefit from cisplatin-based chemotherapy. Age itself should not preclude elderly patients from receiving cisplatin-based chemotherapy. Cisplatin-based combination regimens may be considered as an option in elderly patients with advanced NSCLC.

References