Abstract. Background: Chemotherapy extends life for patients with advanced non-small cell lung cancer (NSCLC). Second-line treatment of NSCLC includes the use of cytotoxic drugs; however, toxicity is of concern. One molecular target for lung cancer is the epidermal growth factor receptor (EGFR). Gefitinib (Iressa™) is an EGFR inhibitor. The aim of our study was to evaluate time to progression (TTP), overall survival (OS) and toxicities in a population affected by NSCLC using Iressa™ as maintenance therapy after first-line chemotherapy. Patients and Methods: Thirty patients were enrolled with stable disease or partial response. Six cycles of a platinum-based first-line chemotherapy were administered. Iressa™ was administered at the dose of 250 mg/d. Results: Median TTP was 5 months; median overall survival was 8 months. TTP for adenocarcinoma and non-adenocarcinoma patients was 10 months and 3.2 months, respectively. No toxic effects were seen in 80% of the patients; 17% of the patients had grade 1 folliculitis. OS for adenocarcinoma and non-adenocarcinoma patients were 15 and 5.9 months, respectively. Conclusion: Gefitinib could be an ideal second-line therapy for adenocarcinoma patients responding to first-line chemotherapy.

Lung cancer is the most common cause of cancer death with the vast majority of patients presenting with non-small cell lung cancer (NSCLC) in advanced inoperable stages. The current first-line treatment for patients with local neoplasms is surgery; by contrast, the first-line treatment for advanced NSCLC includes chemotherapy and palliative radiotherapy, but most patients relapse or progress and eventually succumb to the disease, with 5-year survival rates of approximately 15% for all stages (1). At present, chemotherapy extends life and provides symptom palliation for patients with advanced NSCLC. Normally, no more than 4-6 cycles of first-line chemotherapy are performed. Doublets of drugs are usually administered to patients with good performance status; second-line therapy is controversial, especially in asymptomatic patients who have shown a partial response to first-line treatment. It is not clear when second-line treatment should be started: progression of disease is normally the indicating event, but the response rate is low (about 10-15%), time to progression (TTP) is about 3-4 months and overall survival (OS) does not exceed 8 months after the first-line chemotherapy (2, 3). Current options for the second-line treatment of NSCLC include cytotoxic drugs, such as docetaxel and pemetrexed, and targeted therapies (2-5). Docetaxel was approved in the United States and Europe in 2000 following two Phase III trials that showed the drug’s superiority to the best supportive care alone. Pemetrexed was approved in the United States and Europe in 2004 after a Phase III trial, which showed that, compared with docetaxel, it had comparable activity (median survival time of approximately 8 months in both arms) and a more favorable toxicity profile (4, 6). However, chemotherapy toxicity is of concern: a 5.3% rate of grade 3-4 neutropenia was observed in patients with pemetrexed and a 40.2% rate of grade 3-4 neutropenia was seen in patients with docetaxel, while febrile neutropenia was observed in 1.9% versus 12.7% of patients treated with pemetrexed and docetaxel, respectively (3, 4).

One molecular target of particular relevance to lung cancer pathogenesis is the epidermal growth factor receptor (EGFR), a cell membrane receptor tyrosine kinase. Several inhibitors of EGFR functional activation have been developed. Among these, erlotinib (Tarceva) and gefitinib (Iressa) are two orally bio-available, small molecule EGFR inhibitors of the tyrosine kinase enzymatic activity which prevent EGFR auto-phosphorylation and activation. In monotherapy, each drug has achieved a 10-20% response rate and a 30-50% symptom improvement in previously treated,
chemotherapy refractory, advanced NSCLC patients (7). Furthermore, a randomized, placebo-controlled, multicenter Phase III study reported a two-month improvement in median survival with erlotinib in the second- or third-line treatment of metastatic NSCLC patients (1).

The aim of our study was to evaluate TTP (primary end point), OS and toxicities (secondary end-points) in a patient population affected by NSCLC with partial response or stable disease after first-line chemotherapy and treated with Iressa™ as maintenance therapy immediately after the end of first-line chemotherapy.

Patients and Methods

Patient characteristics. Thirty patients were enrolled in the study. Median age was 66 years (48-75 years); 20 were male (66%), 10 female (34%); 20 were smokers (66%), 10 non-smokers (34%) (according to WHO definitions). Patients had to be under 75 years of age to be enrolled in the study. All patients had stable disease or partial response (RECIST criteria) after first-line chemotherapy. All patients had IV stage NSCLC. Forty-six percent of the patients were affected by adenocarcinoma; 54% were non-adenocarcinoma patients. PS 0-2 (ECOG) was an inclusion criterion, as well.

Treatment plan. First-line chemotherapy was cisplatin (70 mg/m2 d 1 q 21) and gemcitabine (1250 mg/m2 d 1, 8 q 21). Six cycles were administered. Iressa™ was supplied in an expanded access program by Astra-Zeneca and was administered at the oral daily dose of 250 mg/d, 30 minutes before lunch from day 21 of the last course of chemotherapy until progression or toxicity.

In the case of progression (with the exclusion of progressive disease in the brain), second-line salvage chemotherapy was administered (usually weekly docetaxel-33 mg/m2 d 1, 8, 15, q 28) for a maximum of 4 cycles if performance status (PS-ECOG) was 2 or less.

Toxicities. Toxicities were recorded according to NCI-CTC 3.0.

Statistical methods. The Kaplan-Meier method (8) was used to generate survival curves. OS and TTP were defined as the time from the date of the first Iressa™ dose to the date of death from any cause or to the date of disease progression, respectively.

Treatment was considered effective on the assumption that median TTP was similar to or superior to that of second-line chemotherapy (Figure 1); median overall survival was 8 months, similar to that of second-line chemotherapy (Figure 2). No toxic effects were seen in 80% of patients; 17% of patients had grade 1 folliculitis. Anemia, thrombocytopenia nor neutropenia were reported. One patient (3%) had grade 3 diarrhea; this female patient stopped treatment due to the toxic effect, but fully recovered 3 days after treatment interruption. However treatment was discontinued (Table I). Time to progression for adenocarcinoma and non-adenocarcinoma patients was 10 months and 3.2 months, respectively (p=0.002) (Log-rank test) (Figure 3).

OS for adenocarcinoma and non-adenocarcinoma patients was 15 and 5.9 months, respectively (p=0.001) (Log-rank test) (Figure 4).

Discussion

In NSCLC second-line chemotherapy with docetaxel or pemetrexed can palliate symptoms and prolong survival (9). Epidermal growth factor receptor was identified as a candidate for the therapeutic control of cancer more than two decades ago (10). It is expressed in most patients with NSCLC and plays a role in cellular proliferation, inhibition of apoptosis, angiogenesis, metastatic potential and chemoresistance (11). Clinical trials of gefitinib and erlotinib (12-15) have shown the therapeutic viability of targeted agents in NSCLC.

The Iressa™ Dose Evaluation in Advanced Lung Cancer trials (IDEAL 1 and 2) were Phase II randomized studies designed to investigate the efficacy and safety of gefitinib for patients with NSCLC who had previously received one or two chemotherapy regimens, at least one of which contained platinum (12-13). In these trials the responses were much the same with those recorded for patients in chemotherapy trials. These responses were expected to translate into survival benefit.

The Phase III trials of gefitinib, Iressa™ NSCLC Trial Assessing Combination Therapy (INTACT 1 and 2), were designed to assess chemotherapy given concurrently with gefitinib compared to chemotherapy alone in patients with advanced NSCLC who had not received chemotherapy (16-17). Gemcitabine with cisplatin was the chemotherapy applied in INTACT 1, while carboplatin and taxol were used in INTACT 2. Both trials were negative. Gefitinib showed no added benefit in survival, TTP, or RR compared with standard chemotherapy alone.
The Phase III trial IRESSA Survival Evaluation in Advanced Lung Cancer (ISEL) was designed to assess the best supportive care with gefitinib or placebo in previously treated NSCLC patients (18). The results showed a significantly higher objective response rate for patients allocated gefitinib (8% vs. 1%, \( p < 0.0001 \)), but no significant difference between groups in terms of survival. A secondary analysis suggested significance in favor of gefitinib, especially for those with adenocarcinoma.

After the results of the ISEL trial, a Southwest Oncology Group (SWOG) Phase III trial (SWOG 0023) was prematurely closed (19). This trial aimed to assess 250 mg maintenance gefitinib or placebo after radiotherapy plus concurrent platinum or etoposide with consolidation docetaxel. An unplanned interim analysis showed that gefitinib maintenance did not improve survival.

The Second-line Indication for Gefitinib in NSCLC (SIGN) trial was a randomized Phase II trial that assessed gefitinib or docetaxel in patients who failed one or more chemotherapy regimen. Response rate, survival and disease control were similar; toxic effects, however, were higher for docetaxel than for gefitinib, with grade 3-4 toxic effects recorded in 25% of patients receiving the former drug vs. 9% for those on the latter.
None of the above mentioned trials explored second-line and maintenance treatment with gefitinib in patients responding to first-line chemotherapy. By contrast, several trials investigated only patients refractory to previous chemotherapy. Other trials included both responders and non-responders. In our study we included only patients responding to first-line chemotherapy. With maintenance gefitinib our data show a median OS (about 5.7 months) similar to that of second-line chemotherapy patients, with minimal toxicities (20). Shepard et al. showed a median OS with second line chemotherapy with docetaxel of seven months. The TAX 326 trial showed a median OS of six months with monochemotherapy with Vinorelbine, Ifosfamide or Docetaxel with two dosage regimens (21). Other reports confirm these data (22-24). In our trial, however, if we analyze the survival data of adenocarcinoma patients, without regard to smoking or gender, we observe a significant difference in median OS (14.5 months). This is consistent with other reports (25).

On the basis of our findings, gefitinib could be an ideal second-line therapy for adenocarcinoma patients responding to first-line chemotherapy. Admittedly, however, our data are preliminary and require further studies in order to be confirmed. Several ongoing Phase III trials are currently enrolling patients to answer this and other questions about the role of gefitinib in the second-line chemotherapy of NSCLC.

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References


