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Inhibition of EGFR Tyrosine-kinase in NSCLC Treatment: the Hungarian Experience with Gefitinib in the Context of an Expanded Access Programme

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Abstract. *The ZD1839 (Iressa, gefitinib) treatment in phase I trials for patients with advanced non-small cell lung cancer (NSCLC) was associated with disease stabilization and tumor regression. The aim of this study was to analyze the efficacy of gefitinib monotherapy as a second- or third-line treatment for locally-advanced and advanced NSCLC. Data for 50 patients were analyzed. Patients were treated at 5 centers in Hungary as part of the gefitinib Expanded Access Programme (EAP). The response rate was 10% (all partial responses), with disease stabilization in 46% of patients. Disease progression was observed in 44% of patients. The median survival according to the Kaplan-Meier method was 8 months. Median survival of patients with adenocarcinoma was significantly increased compared with squamous cell carcinoma and, of the patients responding to therapy, 80% had adenocarcinoma. The 1-year survival rate was 34%. All patients were evaluable for safety; the adverse events seen with gefitinib were generally mild and only two patients had to be withdrawn from the study due to adverse events. The Hungarian experience suggests gefitinib therapy is effective and well tolerated.*

The development of third-generation cytotoxic drugs (*e.g.* gemcitabine, taxanes, vinorelbine) and their application in platinum-based combination therapy has resulted in considerable progress in the chemotherapy of non-small cell lung cancer (NSCLC) over the past decade. The addition of these agents to single-agent platinum therapy has conferred significant response and survival benefits (1-3). However, such combination regimens have failed to achieve a median survival of 1-year or a response in 50% of patients. Second-line treatment currently includes single-agent therapy using third-generation drugs chosen in accordance with first-line chemotherapy, with docetaxel being the standard treatment (4). No further improvements in efficacy have been observed with cytotoxic chemotherapy in NSCLC, but some improvements in tolerability have been noted; in a phase III randomized study in patients with pretreated NSCLC, pemetrexed treatment resulted in clinically equivalent efficacy outcomes but improved tolerability compared with docetaxel (5). However, it is likely that only new chemotherapeutic methods and principles will result in a significant improvement of outcomes in NSCLC.

A new and promising prospect, which has already been introduced into clinical practice, is molecular-targeted therapy. A potential therapeutic target is epidermal growth factor receptor (EGFR). EGFR tyrosine kinase inhibitors (EGFR-TKI) block signaling pathways in cells, thus curbing cell proliferation, enhancing apoptosis and inhibiting angiogenesis. EGFR-TKIs have been studied in a number of preclinical and clinical trials. The orally active EGFR-TKI gefitinib (Iressa) is the leading agent in this class of novel therapies and has contributed the largest clinical experience, although other agents are in development (erlotinib, CI1033, GW572016, EKB569, PKI166, PD158780, TAK165).

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Based on the results of the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) trials, IDEAL 1 (6) and IDEAL 2 (7), gefitinib was registered first in Japan, then in the USA, and now in over 28 countries worldwide (including Switzerland in Europe) for patients with NSCLC who have previously received chemotherapy. Studies conducted so far have not confirmed that concomitant use of cytotoxic chemotherapy and gefitinib improves therapeutic results (8, 9). In addition to the formal evaluation of gefitinib monotherapy, there is an extensive clinical database of gefitinib use in patients with NSCLC as part of an Expanded Access Programme (EAP), including more than 50,000 patients with NSCLC to date. This article reports the Hungarian experience with gefitinib in this program.

Patients and Methods

Patients were enrolled in the EAP between September 1, 2002 and May 15, 2003 across five centers. All patients provided written, informed consent. Eligibility criteria were as follows: histologically and/or cytologically confirmed NSCLC; progression after prior radiotherapy and/or cytotoxic chemotherapy; ineligibility for cytotoxic chemotherapy; no prior treatment with gefitinib; no prior active malignancy; and performance status (PS): 0, 1 or 2. Women who were pregnant or lactating were ineligible, as were patients receiving concurrent radiotherapy and systemic chemotherapy, or those who had interstitial lung disease. Evaluable patients were those who suffered from locally advanced or advanced NSCLC at the time of enrollement, with expected survival of at least 6 weeks. Of the 50 patients, 30 had received gemcitabine-cisplatin, and 20 patients received cisplatin-etoposid as a first-line treatment. Furthermore, 30 patients received second-line chemotherapy (20 patients, docetaxel monotherapy; 3 patients, paclitaxel monotherapy; 2 patients, gemzar monotherapy; 5 patients, other chemotherapeutic agents).

Patients were treated with a single oral dose of gefitinib 250 mg each day. The first evaluation (based on RECIST criteria) of the patients took place 4 weeks after commencement of gefitinib therapy followed by re-evaluation every 12 weeks on therapy. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). The overall survival time was estimated by the Kaplan-Meier method. This procedure provided an estimation for the median survival time (in weeks). In the second step, the (estimated) median survival times were compared by the Mantel-Haenszel log-rank test for two groups based on sex (men/women) and type of carcinoma (adenocarcinoma/squamous cell carcinoma). The statistical calculations were performed with SAS V8.2 licensed to Planiméter Kft.

Results

A total of 67 patients were enrolled, and 57 patients were evaluable for efficacy, with complete follow-up in 50 patients (7 patients were lost to follow-up). The patient characteristics are shown in Table I. This study cohort had an average age of 60 years and included 29 men (58%). The majority of patients (64%) had stage IV disease, and adenocarcinoma was the predominant in histology (68%). Although the majority of patients had good PS: 0 or 1, 36% had impaired PS: 2.

Table I. *Characteristics of patients.*

	No. of patients (%)
Sex	
Male	29 (58%)
Female	21 (42%)
Average age (range)	60 years (40-76)
Pathology	
Adenocarcinoma	34 (68%)
Squamous cell carcinoma	14 (28%)
Other	2 (4%)
Performance status	
0 or 1	32 (64%)
2	18 (36%)
Disease stage	
III/B	18 (36%)
IV	32 (64%)

The overall disease control rate was 56%, with partial responses in 10% of patients. Stable disease was observed in an additional 46% of patients. Disease progression was documented for 44% of the patients. The median survival was 35 weeks (8 months) (Figure 1), and the 1-year survival rate was 34%. Survival by sex and pathological type are depicted in Figures 2 and 3, respectively; although no difference was seen between men and women, comparison of patients with adenocarcinoma with squamous cell carcinoma patients showed significantly better survival in the adenocarcinoma group ($p=0.039$) (Figure 2). Grade 1 and 2 skin rash was reported in 31% of patients and grade 1 and 2 diarrhea in 12% of the patients (out of 67 patients enrolled). Two patients discontinued treatment due to grade 2 adverse events (alveolitis and severe skin reaction, each in 1 patient). The alveolitis was resolved with steroid treatment and the skin reaction with symptomatic treatment. No grade 3 or 4 adverse events were observed in the patient population during treatment with gefitinib.

Discussion

A new approach to therapy for NSCLC is needed, with a focus on patient-specific therapeutic strategies. Molecular-targeted therapy holds the promise for a major breakthrough in NSCLC therapy. To date, about 170,000 patients with lung cancer have received gefitinib therapy worldwide, including over 50,000 pretreated patients in the EAP.

Evaluation of data from this current cohort of patients receiving gefitinib as part of the EAP reveals a response rate of 10% and stable disease in 46% of patients. The median survival of 8 months and 1-year survival rate of 34%

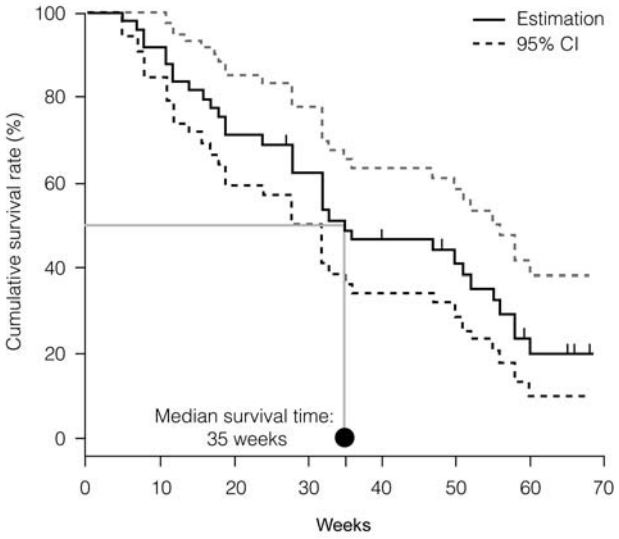

Figure 1. *Kaplan-Meier curves showing overall survival after treatment with gefitinib. The upper and lower lines indicate 95% confidence intervals.*

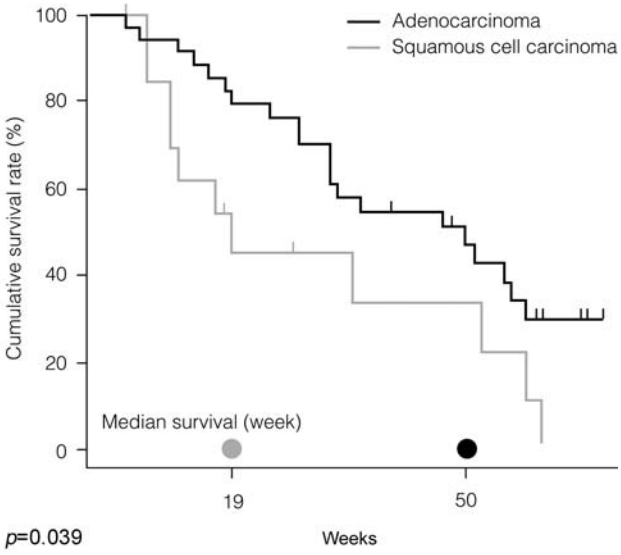

Figure 3. *Kaplan-Meier curves showing overall survival by type of carcinoma after treatment with gefitinib.*

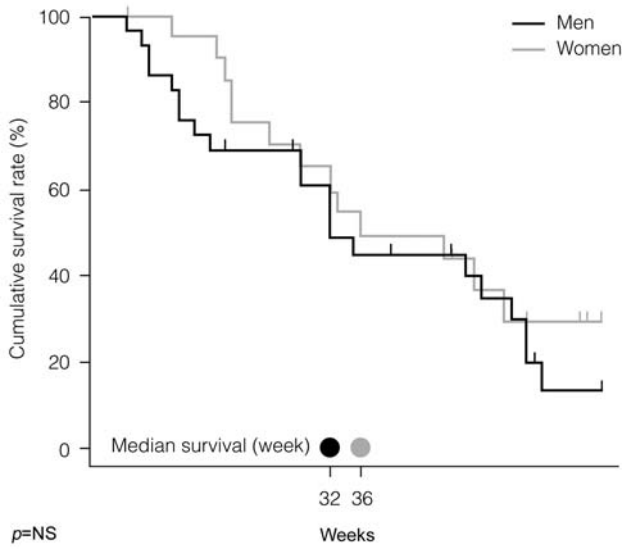

Figure 2. *Kaplan-Meier curves showing overall survival by sex after treatment with gefitinib*

compare favorably with that reported for a large cohort of patients treated in the USA as part of the EAP (10). This study included 21,000 patients and reports a median survival time of 5.3 months, with 1-year survival in 30% of patients. It is worth noting that, while the international experience has provided a substantial body of evidence supporting the good efficacy and favorable tolerability of gefitinib in advanced NSCLC, data from placebo-controlled trials already underway are still awaited.

Recent results have demonstrated a survival advantage for EGFR-TK inhibition compared with best supportive care in pretreated NSCLC (11). In this study, conducted with more than 700 patients, erlotinib demonstrated a statistically significant prolongation of survival compared with placebo. The survival in the erlotinib arm was similar to that observed in studies of gefitinib monotherapy.

Recent studies have demonstrated that a subgroup of patients with NSCLC has specific mutations in the *EGFR* gene, which correlate with dramatic responses to gefitinib (12, 13). However, this does not account for all responses and is unlikely to account for patients who benefit from stable disease. These mutations lead to increased growth factor signaling and confer susceptibility to the inhibitor. Screening for such mutations in lung cancers may identify the patients who will be most responsive to gefitinib. It is anticipated that estimation of the EGFR-TK function, rather than high EGFR expression, will be helpful in the selection of patients with NSCLC for gefitinib therapy.

In conclusion, the Hungarian findings are in accordance with the extensive international experience demonstrating that gefitinib 250 mg daily is an effective second- and third-line treatment of advanced NSCLC. Analysis of the genetic expression pattern of the tumor and establishment of tumor databases will require an increasing involvement of molecular biology in diagnostics. Recognition of signaling pathways and their multi-directional inhibition and appropriate application of cytotoxic and targeted therapy are the way forward. Although we will still not be able to cure patients with advanced NSCLC in the future, at least patient-specific regimens may make it possible to transform

a rapidly progressing fatal disease into a chronic disease, thereby extending the patient's life expectancy by years or even decades.

'Iressa' is a trademark of the AstraZeneca group of companies.

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