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Gefitinib In Pretreated Patients with Advanced Non-Small Cell Lung Cancer - Single Institution Experience

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ABSTRACT

Purpose: To evaluate the activity and tolerability of gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, in pretreated patients with advanced non-small cell lung cancer (NSCLC).

Materials and methods: Thirty-two patients were treated with gefitinib 250mg, orally once daily at our institution between september 2003 and september 2004. The mean age was 62 years (range; 47-85 years). The distribution of patients according to stage was: stage IIIb–19 (59%), and stage IV–13 (41%). Most patients had a baseline Karnofsky performance status of 80,n=16 (50%) or 60-70, n=11 (34%), and had received the following lines of prior chemotherapy regimens: I–3 (9%), II–18 (56%), and III–11 (34%). The mean treatment time was 4.2months (range: 1-12).

Results: There were no complete responses, 7 (22%) patients had partial response, 9(28%)-stable disease and 16(50%)-progressive disease with an overall control of disease in 50% of cases. Overall mean progression free survival was 4.1months (range: 1-12); patients with stage III and IV disease – 5.6months (range: 2-12), and 2.4months (range: 1-6), respectively. skin rash grade 1-2 in 19 patients (59%), grade 1 diarrhea in 6 patients(19%), and hair loss in 1 patient (3%). Were main side effect observed.

Conclusion: Gefitinib demonstrated considerable antitumour activity and a favorable tolerability profile in this series of pretreated patients with advanced NSCLC.

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INTRODUCTION

Lung cancer is the commonest malignancy in men. Despite years of research, the prognosis for patients with lung cancer remains dismal, with a five-year survival rate of 14 percent.[1] Chemotherapy plays an important role for the management of advanced stages of the disease. Standard first-line treatment for patients with unresectable or metastatic NSCLC consists of platinum-based combination chemotherapy, with response rates ranging from 17% to 28% and median survival times ranging from 7.4 to 8.5 months. Patients who failed first-line therapy may benefit from second-line therapy using docetaxel, with response rate 7.1% and median survival 7 months.[2,3]

Treatment option for patients unable to tolerate chemotherapy or failing second line chemotherapy are limited. Survival over three to four years is still a rare event in this disease, and more and more efforts are being made to develop innovative systemic treatment strategies with mechanisms of action different from conventional cytotoxic drugs.

Gefitinib - a small molecule EGF-receptor tyrosine kinase inhibitor - was registered in 2003 by the FDA for the third-line treatment of non-small-cell lung cancer.[4]

The epidermal growth factor receptor (EGFR) mediates cancer cell growth, proliferation, invasion, and metastasis, and inhibits apoptosis. When ligands bind to the receptor, the molecule is phosphorylated by

constitutive tyrosine kinases, causing activation of downstream pathways. Preclinically, drugs targeting these tyrosine kinases block EGFR activation and the intracellular events that follow. Compounds disrupting EGFR tyrosine kinases inhibit the growth of human tumours that express EGFR and cause overexpressing tumours to regress.[5]

The oral drug gefitinib blocks EGFR tyrosine kinases and prevents epidermal growth factor induced proliferation in cell culture. In phase 1 studies of gefitinib given in doses of 150 – 1000 mg per day, the most frequent adverse events were nausea, vomiting, an acneform rash and diarrhoea, the latter two effects becoming dose limiting at the maximum tolerated dose 800 mg per day.[6] Two phase 2 trials of gefitinib monotherapy in patients with pretreated advanced NSCLC demonstrated encouraging activity (objective response rates, 11.8% to 18.4%) and symptom relief (symptom improvement rates, 40.3% to 43.1%) and good tolerability[7]. Phase III trials (the so-called INTACT trials) combined gefitinib and chemotherapy in chemonaive patients with advanced non-small cell lung cancer. These trials failed to demonstrate a survival advantage with the addition of gefitinib to standard platinum-based chemotherapy regimens.

We report here our results of a retrospective analysis of the activity and tolerability of gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, in pretreated patients with advanced non-small cell lung cancer.

Table 1. Patients characterisrics

Patients number -	32
Mean age (years)	62 (range 47-85)
Male/female	25/7 (3.6:1)
KPS: 80 -	16 (50%)
60-70 -	11 (34%)
< 60 -	5 (16%)
Stage: III b -	19 (59%)
IV -	13 (41%)
Prior chemotherapy regimens (number)	
I	3 (9%)
II	18 (56%)
III	11 (34%)
Mean treatment time (Months)	4.2 (range 1-12)

KPS – Karnofsky performance status,

MATERIALS AND METHODS

Between September 2003 and September 2004, 32 patients (Table1) with advanced NSCLC previously treated from one to three chemotherapy regimens, were treated at the Soroka University Medical Center with gefitinib 250mg, orally once daily. The cytotoxic chemotherapy consisted of platinum-based combination regimens with vinorelbine, gemcitabine, or docetaxel. The gefitinib

treatment was begun immediately after chemotherapy failure.

The mean age was 62 years (range: 47-85), male female ratio 3.5:1(25/7). The distribution of patients according to stage was: stage IIIb–19 patients (59%), and stage IV–13pts (41%). Most patients had a baseline Karnofsky performance status of 80 patients or 60-70 (n=16) 1st . The distribution of patients according to lines of prior chemotherapy regimens was: 1st line– 3 patients (9%), II lines – 18 (56%), and IIIrd line –11 patients (34%). The mean treatment time was 4.2 months (range: 1-12).

RESULTS

There were no complete responses, 7 patients (22%) were partial response, 9(28%) - stable disease and 16(50%) - progressive disease with an overall control of disease in 50% of cases. Overall mean progression-free survival was 4.1 months (range: 1-12); patients with stage III and IV patients disease – 5.6 months (range: 2-12), and 2.4 months (range: 1-6) respectively. Main toxicity was: grade 1-2 rash in 19 patients (59%), grade 1 diarrhoea in 6 patients (19%), and hair loss in 1 patients (3%) (Table 2). Summary of treatment results are presented in Tables 3 to histological type of tumour and smoking.

Table 2. Treatment Results

CR	-	0
PR	-	7 (22%)
SD	-	9 (28%)
PD	-	16 (50%)
Mean progression-free survival:		
Stage III	-	5.6 months (range 2-12)
Stage IV	-	2.4 months (range 1-6)
Toxicity		
Skin Rash (grade I-II)		19(59%)
Diarrhoea (grade I)		6(19%)
Hair loss		3(9%)

CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease

Table 3. Patients distribution by histological type, smoking, gender and response rate.

Histology	Smoker			Response rate (%)	
	Male	Female	PR	SD	PD
Squamous cell	11	2	3(23)	3(23)	7(54)
Adenoca	3	-	-	2(67)	1(33)
Large cell	5	1	-	2(33)	4(67)
	Non smoker				
	Male	Female			
Squamous cell	-	-			
Adenoca	6	3	4(44)	2(22)	3(34)
Large cell	-	1	-	-	1(100)

CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease Adenoca adenocarcinoma

DISCUSSION

Cytotoxic chemotherapy treatment options for patients with non-small-cell lung cancer (NSCLC) have limited efficacy and are often associated with significant toxicity. Patients with progressive NSCLC who have been failed by previous chemotherapy have an extremely poor prognosis and often exhibit severe symptoms.

Recent advances in cancer therapy have resulted in the development of drugs that target mechanisms involved in neoplastic change and angiogenesis. One example is gefitinib ("Iressa", ZD1839), an orally-active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that blocks EGFR signaling in vitro, thereby inhibiting the growth, proliferation and survival of many solid tumours.[8] In preclinical studies gefitinib has shown potent activity in a number of tumour models. Two large monotherapy studies (IDEAL 1 and IDEAL 2) in pretreated NSCLC reported a response rate approaching 20% in second-line patients and approximately 10% in those pretreated with two or more chemotherapy regimens.

Female gender, adenocarcinoma, and non smokers were associated with a favorable response.

In our series we reported a response rate of 22% and a disease control rate of 50% with overall mean progression-free survival was 4.1 months (range 1-12). Our results are in line with another studies and support the use of this drug as second- or third-line treatment of advanced NSCLC.[9-11]

However, AstraZeneca has informed physicians and patients that the initial analysis of the primary endpoint of Study 709. IRESSA Survival Evaluation in Lung Cancer (ISEL) with 1692 patients has been conducted, and shows that IRESSA failed to significantly prolong survival in comparison to placebo in the overall population. Full results from ISEL is not published yet. We did not calculate the survival in our analysis and the endpoint was only response rate.

The results of IDEAL-1 and IDEAL-2 indicate that gefitinib monotherapy may offer a single-agent alternative for patients with advanced solid tumours who have received and progressed on prior chemotherapy, many of whom have exhausted their therapy options.

The antitumour activity of gefitinib in patients with advanced NSCLC who have previously received treatment with cytotoxic chemotherapy and non-responders may have positive effect before next line of chemotherapy. We observed in our practice cases of chemosensitization by Iressa after previously chemotherapy failure similar observation have been made by others also[12]. In conclusion gefitinib is a active biological agent and further investigation could lead to improvement in the treatment of NSCLC.

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