PRELIMINARY COMMUNICATION

EFFECTIVENESS OF ERLOTINIB AS A SECOND LINE THERAPY FOR PATIENTS WITH EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION IN NON-SMALL CELL LUNG CANCER (NSCLC): OUR CLINICAL EXPERIENCE

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Abstract: Purpose: The aim of this study was to evaluate tumour response, QoL and adverse effects of erlotinib, EGFR tyrosine kinase inhibitor (TKI), as a second line therapy for patients with EGFR mutation in NSCLC, after failure of previous first-line therapy.

Methods: During the year 2010–11, 5 patients were enrolled in this study for testing EGFR mutations, after conditions for testing were created in Macedonia. We screened 5 patients for EGFR mutations by direct sequencing of exons 18 to 21, by retrospective analysis of their previous biopsy samples. Three of the patients were men and two of the patients were women. Two of the males were former smokers and one male and both females had never smoked. All the patients who were enrolled in the study had histologically proven adenocarcinoma. the patients started with erlotinib 150 mg, one tablet per day, after failure on previous first-line platinum -based chemotherapy, with or without surgery and radiotherapy.

Assessment of tumour response was according to RECIST criteria at the follow-up visits every 4 weeks. We analysed tumour response from the beginning with erlotinib until tumour progression or detection of severe toxicity. Assessment was performed only for those patients with EGFR mutations. Assessment of QoL was performed by patients’ subjective answers, as subjective improvement and without subjective improvements. Adverse effects were applied according to WHO criteria.

Results: Tissue was available for all 5 cases, two (40%) of which were found to harbour an EGFR mutation, identified as exon 19 deletions. Two patients responded to therapy.
A complete response was seen in a female patient for 37 months. Progressive disease was the reason for stopping erlotinib after 37 months and starting third-line therapy. A partial response in one male patient was assessed for 30 months and is still in follow up. This patient is still alive and in good condition. The two patients reported subjective improvements during treatment with erlotinib.

Skin rash was grade 2–3, and diarrhoea was grade 1–2. Both patients complained of hair loss, but without complete alopecia.

Conclusions: Considering our clinical results, we recommend target therapy with erlotinib for patients with NSCLC and EGFR mutations as a second-line treatment. Our excellent results encouraged us to require prospective tissue procurement for all patients in Macedonia. This may in fact require a shift in diagnostic practice, from the current emphasis on fine-needle aspiration, which often provides insufficient material for molecular analysis, to obtaining more substantial biopsies and to provide this treatment as first-line for selected patients.

Key words: erlotinib for second line therapy, epidermal growth factor receptor mutation, tumour response.

Introduction

Lung cancer remains a worldwide epidemic. Approximately 1.2 million people die from lung cancer each year. Non-small cell lung cancer (NSCLC) represents more than 80% of all lung cancers. Most patients with NSCLC presented with stage III or IV disease. Treatment options include chemotherapy with or without radiation and supportive care [1]. Standard first-line chemotherapy for fit patients with advanced NSCLC, results in median overall survival (OS) of 8 to 11 months. the addition of bevacizumab, a targeted monoclonal antibody against vascular endothelial growth factor, to chemotherapy improves survival in a select subgroup of patients with NSCLC [2].

As regards patients who have a relapse on platinum-based chemotherapy, there is a significant need for effective, well-tolerated treatment. Targeted agents such as the orally active epidermal growth factor receptor EGFR tyrosine kinase inhibitor TKI (Erlotinib-Tarceva) and (Gefitinib-Iressa) offered a new therapeutic approach. Discovering somatic EGFR mutations in some patients with NSCLC was a very significant breakthrough in the understanding of this disease. EGFR mutations occur almost within exons 18–21 of the gene of the receptor. Mutations in the EGFR gene lead to the stimulation of oncogenic pathways: tumour progression, proliferation, angiogenesis, invasion and metastatic spread. In the lung cancer setting, it is becoming apparent that NSCLC may not only bea subgroup according to tumour histology but also tumour mutations in
the gene encoding the EGFR. This subgroup of patients appears to confer sensitivity to the EGFR TKI, erlotinib or gefitinib [7].

The aim of this study was to evaluate tumour response, QoL and adverse effects of erlotinib, after failure on first-line chemotherapy in NSCLC patients with EGFR mutations.

**Material and methods**

Patients aged ≥ 18 years with histologically confirmed adenocarcinoma with metastatic spread, failure on first-line platinum based chemotherapy, with or without surgery and radiotherapy were eligible for the study. Patients were required to have measurable disease according to RECIST criteria, life expectancy > 3 months and Eastern Cooperative Oncology Group performance status ≤ 1.

During the year 2010–11, 5 patients were enrolled in this study for testing EGFR mutations, after the provision of conditions for such testing in Macedonia. We screened 5 patients for *EGFR* mutations by direct sequencing of exons 18 to 21, by retrospective analysis of their previous biopsy samples. All the patients had adenocarcinoma. All of the patients were treated with erlotinib 150 mg following failure on first-line chemotherapy, with or without radiotherapy and surgery. In this study we analysed tumour response only in patients with EGFR mutations.

Patients started with erlotinib 150 mg, one tablet per day, after failure on previous first-line platinum-based chemotherapy, with or without surgery and radiotherapy.

Assessment of tumour response was according to the RECIST criteria on the follow-up visits every 4 weeks. We analysed tumour response from the beginning with erlotinib until tumour progression or severe toxicity was detected. Assessment was performed only on those patients with EGFR mutations. Assessment of QoL was performed by patients’ subjective answers, subjective improvement or without subjective improvements. Adverse effects were performed according to WHO criteria. Detection of EGFR mutations by direct sequencing, and reporting the results were performed by the Faculty of Pharmacy in Skopje, Macedonia (Figure 1).
Figure 1 – Patient report with mutation on EGFR gene-deletion of exon 19
Results

Three of the patients were men and two of the patients were women. Two of the male patients were former smokers and one male patient and both of the female patients had never smoked. All the patients who were enrolled in the study had histologically proven adenocarcinoma. Patient characteristics are presented in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
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<tr>
<td><strong>ADENOCARCINOMA</strong></td>
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We detected two patients with EGFR mutations. One patient was a man with dissemination of lung cancer disease in both lungs. After failure on first-line chemotherapy with Carboplatine/Gemcitabine schema, erlotinib 150 mg per day was started. He presented PR (partial response) for 30 months and he is still alive (Picture 1). He reported subjective improvement during treatment.

Another patient was female. Her disease progressed after 4 cycles of chemotherapy with Paclitaxel/Carboplatin. Disease dissemination was assessed in the brain and both lungs. Tumour response from beginning with erlotinib presented with CR (complete response) was detected for 37 months (Picture 2). The patient reported subjective improvement during treatment with erlotinib. This patient presented PD (progressive disease) after 37 months.

Common adverse events were skin rashes in both patients graded 2–3 and diarrhoea graded 1–2 according to WHO criteria (Picture 3). No patient was withdrawn from the study because of the adverse events.
9.9.2009

Picture 1 – Partial response of male patient treated with erlotinib

18.11.2009

Picture 2 – Complete response of female patient treated with erlotinib

Discussion

In 2004, two independent studies discovered an underlying association between mutations in the EGFR TK domain and gefitinib-responsive NSCLC [3, 4]. Dramatic drug response might be associated with mutational alterations in the drug target, and indeed we found that eight of nine responsive cases had an EGFR mutation, compared with zero of seven unresponsive cases ($p < 0.001$) [3]. In a screening for kinase mutations in untreated NSCLC cases, Paez et al. [4] observed EGFR mutations predominantly in tumours from Asian patients and found mutations in five of five gefitinib-responsive cases. Pao et al. extended these findings to erlotinib-responsive cases [5]. Mutations are more common in non-smokers, women, Asians, and patients with adenocarcinoma [4, 5].

We examined only 5 patients after conditions for such testing were created in Macedonia. We assessed 2 patients with proven EGFR mutation status, and they had a remarkable tumour response, compared with second-line chemotherapy. The overall rate of complete or partial response to erlotinib was 70.6% in retrospective and prospective studies. The higher probability of response was
associated with the deletion of exon 19 and in patients between the ages of 61 and 70. Median overall survival was 27 months, which is an improvement compared with chemotherapy, yielding 30% response and low median survival [6–8]. These results showed that EGFR-mutant lung cancer is a distinct class of NSCLC.

Conclusions

In conclusion, screening for EGFR mutation should be encouraged in women, in those who have never smoked and in those with non-squamous lung tumours in R. Macedonia. This may in fact require a shift in diagnostic practice, to obtaining more substantial biopsy samples and to provide TKI as a first line for pts with EGFR mutations.

Considering our clinical results, we recommend target therapy with erlotinib for patients with NSCLC and EGFR mutations as a second-line treatment.

REFERENCES

Резиме

ЕФИКАСНОСТА НА ЕРЛОТИНИБОТ КАЈ БОЛИН СО НЕМИКРОЦЕЛУЛAREN БЕЛОДРОБЕН КАРЦИНОМ КОИ ИМААТ МУТАЦИИ НА РЕЦЕПТОРОТ ЗА ЕПИДЕРМАЛЕН ФАКТОР НА РАСТ: НАШИ ИСКУССТВА

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Апстракт: Целта на студијата е да се евалуира туморскиот одговор, квалитетот на живот и несаканитите ефекти од третманот со ерлотиниб, кај болни со немикроцелуларен белодробен карцином кои имаат мутацији на рецепторот за епидермален фактор на раст (EGFR), откако за ова испитување се создадо услови во Македонија. Во текот на 2010–2011 година пет болни се тестирани за мутацији на EGFR, откако за ова испитување се создадо услови во Македонија. Преку ретроспективна анализа на нивните патохистолошки примероци, ја детектирани мутацијата на рецепторот на ЕГФ со методата на директно секвенцирање на аксоните од 18 до 21. Сите болни беа со доказан белодробен карцином, тројца беа мажи и две жени. Двајца од мажите беа пуцачи, а двете жени и единот маж, непушачи. Сите болни започнуваа терапија со ерлотиниб, една таблета на ден, по прогресија на болеста на прва линија на хемотерапија. Се оценувала туморскиот одговор, квалитетот на живот и несаканите ефекти од спроведената терапија со ерлотиниб.

Кај двајца од вкупно пет болни се детектирани мутација во вид на делчта на ексовот 19. Комплетен одговор се оцени кај болнатата жена во трење од 37 месеци. Кај болнатиот маж оценет е парцијален одговор во трене од 30 месеци и тој е сè уште жив. Со оглед на овие клинички резултати и не го препорачуваме ерлотинибот за втора линија на терапија. Со ова би ја подобриле досегашната дијагностичка пракса кај белодробниот карцином, со добивање на примероци кои нудат можност за испитување на мутацији на факторот на раст. Би требало оваа група на болни со позитивни мутации, да се издвои како посебна и за неа да се обезбеди целна терапија уште во првата линија.

Клучни зборови: втора линија на терапија, епидермален фактор на раст-мутиации, туморски одговор.

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