Do NSCLC patients become sensitive to second-line erlotinib treatment after previous radiotherapy?

Czy pierwszorzutowa radioterapia może uwrażliwiać chorych z niedrobnokomórkowym rakiem płuca na erlotynib stosowany w drugiej linii leczenia?

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Kardiochirurgia i Torakochirurgia Polska 2010; 7 (4): 411–414

Abstract

Background: Erlotinib is an EGFR tyrosine kinase inhibitor (EGFR-TKI) that has shown activity in recurrent NSCLC. One could speculate that sensitivity to erlotinib is dependent on the activated form of *EGFR* gene mutation in tumour cells. The radiation-induced activation of the EGFR pathway and *EGFR* gene mutation in cancer cells could arouse the response to EGFR-TKI agents.

Aim: The aim of the study was to evaluate the effectiveness of erlotinib in second- and third-line therapy according to the type of first-line therapy.

Material and methods: 102 patients with recurrent NSCLC, who had erlotinib administered in second- and third-line therapy, were divided into two groups: group A – included patients treated first-line with a combination of thoracic radiotherapy and cisplatin-based chemotherapy (n = 40); group B – patients treated with chemotherapy alone (n = 62). The efficacy of erlotinib was analysed based on chi-square, Cox logistic regression and Kaplan-Meier tests.

Results: Disease control and survival longer than 6 months during erlotinib administration were observed significantly more frequently in patients from Group A than from Group B ($p < 0.05$ and $p < 0.005$, respectively). Median time of overall survival was 16 months for Group A and only 5 months for Group B. Moreover, probability of survival was significantly higher in Group A than in Group B ($p < 0.005$, HR = 2.179, 95% CI: 1.339-3.546). Based on the Cox regression model, among 6 other prognostic factors, no application of radiotherapy in first-line treatment had a significant impact on the reduction of overall survival ($p < 0.005$, HR = 2.636, 95% CI: 1.385-5.015).

Conclusions: Our observations indicate that application of radiotherapy in first-line treatment has predictive rather than prognostic value for the efficacy of erlotinib second- or third-line therapy.

Streszczenie

Wstęp: Erlotynib jest inhibitorem kinazy tyrozynowej EGFR (IKT-EGFR) stosowanym w leczeniu nawrotowego, zaawansowanego, niedrobnokomórkowego raka płuca (NDRP). Wydaje się, że wrażliwość komórek nowotworowych na działanie erlotynibu jest zależna od występowania w nich mutacji genu *EGFR*. Zwiększenie prawdopodobieństwa odpowiedzi na leczenie IKT-EGFR w NDRP może zależeć od aktywacji szlaku sygnałowego EGFR oraz wystąpienia mutacji genu *EGFR* pod wpływem wcześniejszej radioterapii.

Cel pracy: Celem pracy była ocena skuteczności erlotynibu w drugiej i trzeciej linii leczenia NDRP w zależności od rodzaju pierwszej linii leczenia.

Materiał i metody: 102 chorych leczonych z powodu nawrotowego NDRP za pomocą erlotynibu zostało podzielonych na dwie grupy. Grupę A stanowili pacjenci otrzymujący w pierwszej linii leczenia radioterapię i dwulekową chemioterapię opartą o związki platyny (n = 40). W grupie B znaleźli się chorzy leczeni w pierwszej linii wyłącznie dwulekową chemioterapią z udziałem związków platyny (n = 62). Skuteczność erlotynibu została oceniona za pomocą testu chi-kwadrat, modelu regresji logistycznej Coxa i metodą Kaplana-Meiera.

Wyniki: Kontrola choroby oraz przeżycie dłuższe niż 6 mies. po zastosowaniu erlotynibu było obserwowane istotnie częściej wśród chorych z grupy A niż z grupy B (odpowiednio: $p < 0,05$ i $p < 0,005$). Mediana całkowitego czasu życia wynosiła 16 mies. w grupie A i tylko 5 mies. w grupie B. Prawdopodobieństwo przeżycia ocenione metodą Kaplana-Meiera było także znacznie wyższe w grupie A niż w grupie B ($p < 0.005$, HR = 2,179, 95% CI: 1,339–3,546). Na podstawie modelu regresji logistycznej Coxa stwierdzono, że wśród 6 istotnych czynników ryzyka skrócenia całkowitego czasu życia chorych leczonych erlotynibem brak zastosowania radio-

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Key words: radiotherapy, erlotinib, non-small cell lung cancer, predictive factor.

terapii w pierwszej linii leczenia znacząco zwiększa to ryzyko ($p < 0,005$, HR = 2,636, 95% CI: 1,385–5,015).

Wnioski: Nasze obserwacje wskazują, że możliwość zastosowania radioterapii w pierwszej linii leczenia stanowi korzystny czynnik predykcyjny dla terapii erlotynibem w leczeniu drugiego lub trzeciego rzutu chorych na NDRP.

Słowa kluczowe: radioterapia, erlotynib, niedrobnokmórkowy rak płuca, czynnik predykcyjny.

Introduction

Thoracic radiotherapy (RT) in combination with chemotherapy is standard first-line treatment for locally advanced or unresectable non-small cell lung cancer (NSCLC) patients. However, chemotherapy alone is applied for patients with metastatic NSCLC. The addition of RT to cisplatin-based chemotherapy results in further tumour growth inhibition, lengthening disease-free survival and overall survival but, in most cases, does not ensure complete recovery of patients [1].

Erlotinib is an EGFR tyrosine kinase inhibitor (EGFR-TKI) that has shown activity in recurrent NSCLC. The objective response for erlotinib treatment occurs only in about 10% of Caucasian patients. Sensitivity to EGFR-TKI is dependent on the activated form of *EGFR* gene mutation in tumour cells. Molecular abnormalities occur more frequently among never-smoking female patients with adenocarcinoma [2, 3]. Nevertheless, independent predictive factors for unambiguous qualification for EGFR-TKI treatment have not been assessed [4].

The randomised trials evaluating the effectiveness of EGFR-TKI therapy as an addition to radiotherapy in head and neck cancer indicated that this combination of therapy significantly improves the outcome of radiotherapy [5]. High level of EGFR protein expression is correlated with resistance to radiation therapy in a variety of cancers, mostly in squamous cell carcinoma of the head and neck. Moreover, susceptibility to radiation therapy is improved by blockage of the EGFR domain by EGFR-TKI agents [6, 7]. An individual case report showed that erlotinib-induced skin rash could spare skin irradiated in previous RT [8]. Moreover, *EGFR* gene mutation is an independent, good predictive factor for response to whole-brain radiation therapy in adenocarcinoma metastases [9]. However, the radiation-induced activation of the EGFR pathway and *EGFR* gene mutation in cancer cells could stimulate the response to EGFR-TKI agents [7]. Finally, we could not clearly state whether erlotinib is more effective in recurrent NSCLC patients after radiotherapy combined with chemotherapy than after chemotherapy alone.

Material and methods

Locally advanced and advanced NSCLC patients ($n = 102$) treated with erlotinib (150 mg per day) in second- and third-line therapy were divided into two groups: Group A included patients treated first-line with a combination of thoracic radiotherapy and cisplatin-based chemotherapy ($n = 40$). The patients treated with chemotherapy alone ($n = 62$) were classified into Group B. The patients' characteristics are presented in Table I.

The chi-square test and Cox regression model were used to test potential predictive and prognostic factors that affected clinical response and overall survival. The Kaplan-Meier method was used for the comparison of survival probability in different groups. The following predictive and prognostic factors were included in the analysis: age, gender, smoking status, performance status (ECOG-WHO), weight loss, anaemia, serum LDH level, histopathological diagnosis, initial stage of disease, stage of disease (IIIB or IV), time from diagnosis to erlotinib treatment, response to first-line treatment, progression-free survival after first-line treatment, erlotinib therapy toxicity (rash), EGFR protein expression by immunohistochemistry method (in 29 patients), *EGFR* gene copy number by FISH method (in 23 patients) and *EGFR* gene mutation status (exon 19 and 21) by allele-specific refractory mutation PCR method (ARMS-PCR) and DNA fragment length analysis (in 26 patients).

Results

Group A and Group B were well matched, except for histopathological diagnosis and clinical response to first-line treatment. Group A had fewer adenocarcinoma-bearing patients than Group B ($p < 0.05$). However, disease control after first-line treatment was observed significantly more frequently in Group A than in Group B ($p < 0.05$). Progression-free survival was longer, but not significantly ($p = 0.07$), for Group A than Group B (Table I). Moreover, the initial stage of NSCLC was different between these two groups. Locally advanced lung cancer was diagnosed initially only in 18 patients from Group B.

Disease control and survival longer than 6 months during erlotinib administration were observed significantly more frequently in patients treated with both RT and chemotherapy than in patients who received only chemotherapy in first-line treatment ($p < 0.05$ and $p < 0.005$, respectively). This observation was applied only to patients with stable disease (Table I). Neither expression of EGFR protein nor amplification of the *EGFR* gene, but the presence of *EGFR* gene mutation ($p < 0.05$, $\chi^2 = 7.094$) significantly reduced the risk of early progression in erlotinib-treated patients. Clinical factors which affected the risk of early progression were similar to factors specified in clinical trials, e.g. BR.21. However, response to first-line treatment and stage of disease had no

Tab. I. Characteristics of patients treated with erlotinib according to type of first-line therapy

	Group A (chemotherapy + radiotherapy)	Group B (only chemotherapy)	*p* χ^2
Whole group	40	62	
Gender (median age – years)			
Male	23 (57.5%, 60.5 yr)	44 (71%, 61.0 yr)	0.236
Female	17 (42.5%, 60.0 yr)	18 (29%, 66.0 yr)	1.405
Smoking status			
Smokers (pack-years)	29 (72.5%, 38)	46 (74.2%, 40)	0.968
Never smokers	11 (27.5%)	16 (25.8%)	0.002
Performance status			
PS = 0 or 1	19 (47.5%)	23 (37.1%)	0.403
PS = 2 or 3	21 (52.5%)	39 (62.9%)	0.699
Histopathology			
Adenocarcinoma	18 (45%)	43 (69.3%)	**0.0249**
Other types of NSCLC	22 (55%)	19 (30.6%)	**5.029**
Disease stage*			
III B	14 (35%)	14 (22.6%)	0.252
IV	26 (65%)	48 (77.4%)	1.311
Response to first-line treatment			
CR, PR, SD (median PFS – months)	34 (85%, 8.5 mo)	37 (59.7%, 6 mo)	**0.0126**
PD	6 (15%)	25 (40.3%)	**6.221**
			0.0699**
Response to erlotinib treatment			
Disease control (PR + SD)	18 (45%)	13 (21%)	**0.0185**
Early progression (PD)	22 (55%)	49 (79%)	**5.55**
Response to erlotinib treatment			
Partial response (PR)	4 (7.5%)	6 (9.7%)	**0.0167**
Stable disease (SD)	14 (35%)	7 (11.3%)	**8.181**
Early progression (PD)	23 (57.5)	49 (79%)	
6-months survival of erlotinib-treated patients			
Yes	23 (57.5%)	17 (27.4%)	**0.0047**
No	17 (42.5%)	45 (72.6%)	**8.011**
Rash			
Yes	16 (40%)	25 (40.3%)	0.862
None	24 (60%)	37 (59.7%)	0.0304
EGFR* gene mutation status**			
Mutation in exon 19 or 21	2 (5%)	3 (4.9%)	
None	7 (17.5%)	14 (22.7%)	0.799
Unknown	31 (77.5%)	43 (69.4%)	0.499

**at the beginning of erlotinib treatment; **for comparison of median PFS (Mann-Whitney U test); ***at the moment of initial diagnosis (before first-line treatment)*

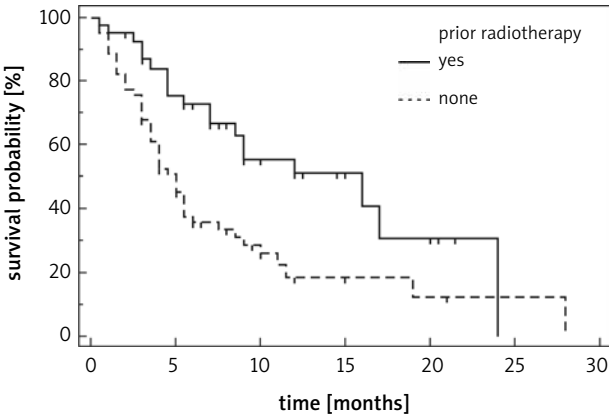
significant influence on the risk of early progression or on survival time shortening.

The median time of overall survival measured from the beginning of erlotinib treatment was 16 months for Group A and only 5 months for Group B. Probability of survival was significantly higher in Group A than in Group B ($p < 0.005$, HR = 2.179, 95% CI: 1.339-3.546, Fig. 1). Moreover, survival probability was significantly higher for patients with disease control after first-line treatment compared to patients with early progression ($p < 0.005$, HR = 2.045, 95% CI: 1.163-3.596).

Based on the Cox regression model with stepwise selection procedures by minimum AIC, we established 6 prognostic risk factors of overall survival shortening for erlotinib-treated patients: poor performance status ($p < 0.0001$, HR = 4.937, 95% CI: 2.601-9.369), heavy smoking ($p < 0.0005$, HR = 3.614, 95% CI: 1.765-7.398), lack of radiotherapy in first-line treatment ($p < 0.005$, HR = 2.636, 95% CI: 1.385-5.015), rash at the beginning of the erlotinib treatment ($p < 0.005$, HR = 2.478, 95% CI: 1.336-4.595), weight loss > 5% ($p < 0.01$, HR = 2.225, 95% CI: 1.247-3.969) and time from diagnosis to erlotinib treatment ($p < 0.05$, HR = 2.084, 95% CI: 1.14-3.807). Overall model fit was as follows: $p < 0.0001$, $\chi^2 = 73{,}769$. Overall survival did not significantly depend on response to first-line treatment or disease stage (both initial and during erlotinib treatment).

Conclusion

In most clinical trials prior cisplatin-based chemotherapy was a necessary requirement for qualification for second- and third-line therapy with erlotinib in recurrent NSCLC [2].



number at risk

group: yes						
40	27	13	5	2	0	0
group: none						
62	24	7	3	2	1	0

Fig. 1. Patients' survival probability according to the possibility of radiotherapy application in first-line treatment of NSCLC patients

The role of RT in probability of response to erlotinib first-line treatment was not carefully considered. Generally, it was ascertained that the response to first-line chemotherapy has an impact on response to erlotinib in second- or third-line treatment. It is established that the application of both chemo- and radiotherapy gives better results than chemotherapy alone [1]. In the light of these conclusions we have to face the question: does the radiotherapy or rather the response to first-line treatment have predictive and prognostic value in erlotinib second- or third-line therapy outcome?

In this report we have shown that application of radiotherapy and chemotherapy in first-line treatment results in higher probability of disease control after erlotinib treatment as well as in the prolongation of overall survival. Consequently, this combination of therapy has a predictive and prognostic impact on erlotinib treatment.

One could speculate that RT can induce the *EGFR* gene mutation and activate carcinogenesis through the EGFR pathway. It would be advisable to examine the *EGFR* gene mutation before and after radiotherapy.

On the other hand, a lower percentage of adenocarcinoma in an initial lower stage of cancer was observed in the group of patients who were treated with thoracic radiotherapy, which distinguishes them from the group of patients treated with chemotherapy alone. The differences in natural disease course may have a crucial prognostic role. It was confirmed by the high percentage of patients with stable disease (but not with response) after erlotinib therapy in the group of patients treated with a combination of radiotherapy and chemotherapy in first-line treatment. However, these factors were of lower significance concerning erlotinib effectiveness than the application of radiotherapy in first-line treatment. Moreover, a histopathological diagnosis other than adenocarcinoma should be associated with poorer response to erlotinib therapy. In conclusion, our observations indicate that application of radiotherapy in first-line treatment has predictive rather than prognostic value for the efficacy of erlotinib second-line therapy.

Competing interests

The authors declare that they have no competing interests.

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