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Efficacy and influence factors of icotinib hydrochloride in treating advanced non-small cell lung cancer

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Abstract. – OBJECTIVE: To evaluate the efficacy and safety of icotinib hydrochloride in the treatment of patients with advanced non-small cell lung cancer (NSCLC) and discuss the influence factors on efficacy.

PATIENTS AND METHODS: 120 treatment-experienced patients confirmed by pathology or cytology with stage III B-IV non-small cell lung cancer took icotinib hydrochloride and erlotinib orally until the occurrence of disease progression or serious adverse reactions. Then, the efficacy of icotinib hydrochloride and the related influence factors were analyzed.

RESULTS: In icotinib hydrochloride group, the response rate and the disease control rate were 30.00% and 65.00%, and the median progression-free survival time was 179 days (95% CI: 103.21-254.78); in erlotinib group, the response rate and the disease control rate were 25.00% and 56.70%, and the median progression-free survival time was 121 days (95% CI: 95.05-146.94). Moreover, the objective response rate and the disease control rate of second-line therapy were both superior to the third-line and above therapy. The objective response rate of patients with complete response/partial response/stable disease after the first-line therapy was higher than that of patients without response after the first-line therapy ($p<0.05$), and the significant differences existed in the objective response rate and the disease control rate among mutant group, wild-type group, and unknown group ($p<0.05$). The response rate and the disease control rate of erythra group were higher than those of non-erythra group ($p<0.05$). It was showed in the univariate analysis that the progression-free survival was correlated with the smoking status and the epidermal growth factor receptor gene mutations.

CONCLUSIONS: The icotinib hydrochloride is effective and safe in treating the treatment-experienced patients with advanced NSCLC, especially for patients with sensitive mutations.

Key Words:
Icotinib hydrochloride, Non-small cell lung cancer, Efficacy, Safety, Erlotinib.

Introduction

In the most parts of the world, the lung cancer ranks on the top list between global tumor occurrence and mortality, which seriously threatens the human health and life. Lung cancer mainly includes non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), in which NSCLC accounts for 80% and has a five-year survival rate of only 12-15%[1,2]. Due to the occult features of lung cancer at the early stages, over 70% patients with lung cancer have missed the chance of surgery when they felt ill. Moreover, less than 1/3 NSCLC patients are early diagnosed and subjected to excision. Although the traditional chemotherapy can reduce mortality to some extent, it just only increases the one-year survival rate from 20% to 29%[3]. Also, the traditional chemotherapy has great toxicity and side effects that are intolerable for advanced patients with poor health conditions. Before application of the targeted therapy to clinical treatment, the systemic chemotherapy was the primary method of treating advanced NSCLC. However, with the development of molecular biology and further study of tumor signal transduction, the targeted therapy has been a significant method[4]. Epidermal growth factor receptor (EGFR) is a major signal transduction pathway, which regulates onset, growth and apoptosis of tumor, and it was turned out in many studies that NSCLC with EGFR mutants has special clinical characteristics and progressions. The epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been widely applied to the second-line therapy of advanced NSCLC. Through working on the epidermal growth factor receptor tyrosine kinase, it was discovered that the EGFR can block the signal transduction to inhibit tumor growth, thereby prolonging the life of patients, especially lung cancer patients with

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EGFR mutants[5-7]. As the convenient way takes mild adverse reactions with better tolerance than the second-line therapy, its representative medicines gefitinib and erlotinib have been widely used in clinical treatment for superior clinical trial results at Stage III[8]. As the third single target EGFR-TKI clinically applied to the treatment of advanced NSCLC, icotinib hydrochloride was the first Chinese small molecular targeted anti-cancer drug with the independent intellectual property rights, and it is an effective and specific EGFR-TKI[9]. The basic research and clinical trial suggested that icotinib hydrochloride and gefitinib were similar in chemical structures, molecular mechanisms, efficacies and other aspects; Phase III clinical trial, ICOGEN, proved equivalent clinical efficacy of both drugs in the second-line and third-line therapy of NSCLC, but the icotinib hydrochloride was superior in safety aspect[8]. Besides, a clinical observation indicated that the icotinib highlighted sounds efficacy and safety in treating advanced NSCLC patients. In this study, advanced NSCLC patients who have complete clinical data upon treatment of icotinib hydrochloride or gefitinib from March 2010 to March 2016 were recruited to the retrospective analysis of efficacy, safety, and the exploration of risk factors.

Patients and Methods

Inclusion criteria and exclusion criteria

The inclusion criteria: (1) Patients in phase III-B or IV NSCLC confirmed by histology or cytology (according to the 7th Edition TNM clinical staging criteria of NSCLC by IASLC); (2) Patients with recurrence during or after the first-line therapy; (3) At least one evaluable target lesion; (4) Aging between 18-80 years old; (5) All patients have voluntarily signed the informed consent.

The exclusion criteria: (1) Lymphatic metastasis; (2) No evaluable lesion; (3) Other TKI taking history; (4) Radiotherapy and chemotherapy intolerance; (5) Using other drugs during medication without permission; (6) With history of mental illness, unable to cooperate with treatment, or being followed up; (7) Interstitial pneumonia; (8) The patient's last chemotherapy to this trial was less than three weeks, and still suffered from toxics and side effects with chemotherapy; (9) The life expectancy was less than 12 weeks; (10) Incomplete clinical data.

Clinical data

From March 2010 to March 2016, 120 patients met the above inclusion and exclusion criteria. The clinical data includes: sex, age, pathological type, tumor stage, smoking history, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and chemotherapy history, etc. Before the treatment, all patients were subjected to examinations of blood routine, liver and kidney function, chest CT, abdominal color Doppler ultrasound, head CT or MRI and bone scan (Thermo Fisher Scientific, Waltham, MA, USA) as well as evaluation of ECOG PS score. The above indicators were checked regularly during the medication period, and the imaging examination was carried out after 1 month, then once in every 2 months until they had disease progression or adverse reactions for intolerance. Among the 120 cases, there were 44 females and 76 males, aged 44-80 (62.54±12.63) years old. For case stages, there were 41 cases of phase III B and 79 cases of phase IV. For tumor types, there were 84 cases of adenocarcinoma, 27 cases of squamous carcinoma, 6 cases of squamous adenocarcinoma and 3 cases of other types. By random number table, all cases were evenly divided into two groups, the experimental group (60 cases) and the control group (60 cases). The process of patients' recruitment and follow-up were shown in Figure 1. The study had been approved by Ethical Committee of Henan Tumor Hospital. All patients had signed the informed consent.

Methods

Patients in the experimental group orally took icotinib hydrochloride (Beida Pharmaceutical Co., Ltd, Hangzhou, Zhejiang, China) (H20110061, specification: 125 mg) three times a day and 125 mg every time until they had disease progression or intolerance. Due to the side effects, 2 cases reduced dose to two times a day and 125 mg in each time for one month, and after that they were back in normal dose again. Patients in the control group orally took erlotinib (Roche Registration Ltd, Welwyn Garden City, Hertfordshire, UK) (H20120101) once a day and 100 mg in every day. During the treatment, patients received neither anti-tumor treatment except for important treatment nor palliative radiotherapy except for the reason of releasing pain.

Evaluation criteria

The Response Evaluation Criteria in Solid Tumor (RECIST) was employed to evaluate the efficacy. The first efficacy evaluation was performed in the

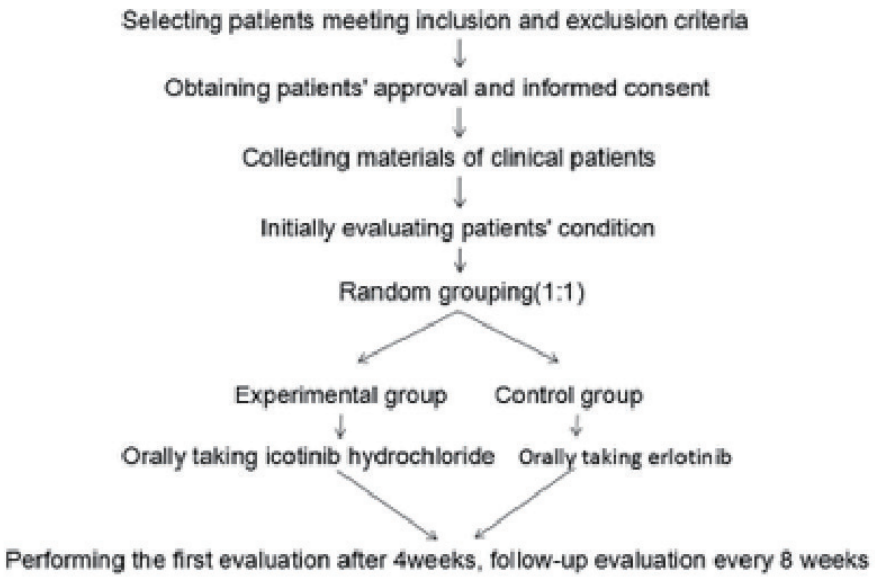

Figure 1. Patient recruitment and follow-up.

fourth week after the medication, after which the efficacy evaluation was conducted every eight weeks (less than one week between every two evaluable periods). The overall efficacy was divided into the complete response (CR), the partial response (PR), the stable disease (SD) and the progressive disease (PD). The objective response rate (ORR) was calculated by CR and PR, the disease control rate (DCR) was calculated by CR, PR and SD. The progression-free survival (PFS) refers to the interval time from the start of treatment to the progression of disease or death or end of follow-up caused by any reason. The toxicities and side effects were assessed in accordance with the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) 3.0.

Statistical Analysis

SPSS19.0 statistical software (SPSS Inc., Chicago, IL, USA) was adopted to deal with data and statistical analysis. Factors related to efficacy were analyzed by X^2 test and Fisher exact test. Kaplan-Meier method was employed to carry out survival analysis and Log-Rank test for difference significance. $p<0.05$ indicates statistical difference and $p>0.05$ indicates the opposite.

Results

Comparison of Clinical Data between the Two Groups

Differences between the two groups in sex, age, pathological stage, pathological type, tumor location, as well as gene mutation had no statistical significance, as shown in Table I.

Comparison of Clinical Efficacy Between the two Groups

There was no loss or withdrawal of patients during the treatment. The ORR was 30.00% in

Table I. Comparison of clinical data between the two groups.

Group	Sex (male/female)	Age/years old	Pathological stage (phase III B/IV)	Pathological type (adenocarcinoma/squamous carcinoma/ squamous adenocarcinoma/others)
Treated group	37/23	62.38±12.28	19/41	43/13/3/1
Control group	40/20	62.77±12.96	22/38	41/14/3/2
t/χ^2	0.326	1.698	0.333	0.418
p	0.568	0.187	0.564	0.937

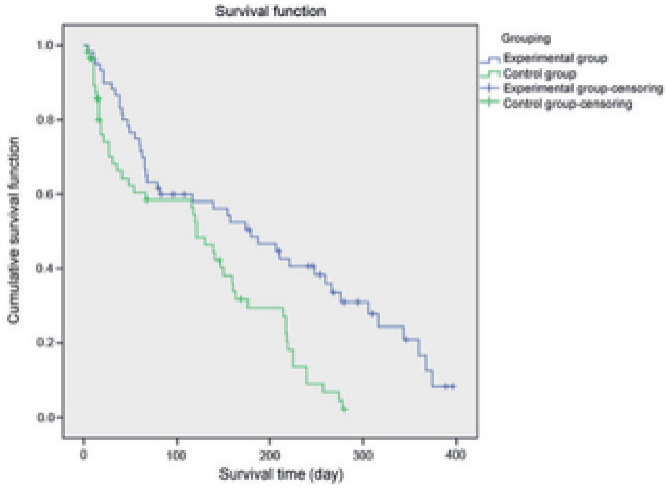

Figure 2. Kaplan-Meier survival curves of the two groups.

the experimental group and 25.00% in the control group, and the difference between the two groups had no statistical significance (p>0.05). The six-month DCR was 56.70 % in the control group and 65.00% in the experimental group and their comparison had no statistical significance, either (p>0.05), as shown in Table II. The median PSF of the experimental group was 179 days (95% CI: 103.21-254.78) and that of the control group was 121 days (95% CI: 95.05-146.94) and the comparison indicated that χ^2=11.08, p=0.01 (see Figure 2).

Efficacy Analysis of Advanced NSCLC Patients upon Treatment of Icotinib Hydrochloride

According to X^2-test, the ORR of the female patients was higher than that of the male patients. Both ORR and DCR of patients with the second-line therapy were higher than those of patients with the third-line and above therapy; ORR of patients with CR/PR/SD after the first-line therapy was higher than that of patients without response after the first-line therapy. The difference in the comparison of ORR and DCR between patients with erythra and without erythra was statistically significant; and the difference of the comparisons of ORR and DCR among mutation group, wild-type group and the unknown group were statistically significant. Moreover, the difference of the comparison of DCR between patients with or without the brain metastasis was statistically significant as well; while the comparisons of ORR and DCR among patients aged less or no less than 65 years old, with PS score between 0-1 or no less than 2, smoking or not smoking, as well as with adenocarcinoma or squamous carcinoma, had no statistically significant difference. Results were shown in Table III.

Analysis of PFS and the Correlative Factors

As of the date of follow-up, PSF of 60 patients was not related to sex, age, PS score, pathological type, the second or third line therapy, the first-line therapy, erythra, mutation site and whether having brain metastases, but related to EGFR gene mutation and smoking status. Median PSF of mutation type was 195 days (95% CI: 73.25-288.12) and that of feral and unknown type was 88 days (95% CI: 11.63-157.53), and

Table II. Subgroups' analysis results.

	OR	Sens	Spec	PLR	NLR	DOR	AUC
Serum	28.38(15.37-52.40)	0.87(0.79-0.95)	0.86(0.82-0.89)	6.2(4.8-8.0)	0.15(0.09-0.25)	41(22-77)	0.90(0.87-0.92)
Plasma	7.90 (4.75-13.15)	0.83(0.75-0.89)	0.61(0.54-0.68)	2.1(1.8-2.5)	0.28(0.19-0.4)	8(5-12)	0.76(0.72-0.79)
Tissue	18.32 (3.91-85.88)	0.83(0.78-0.87)	0.70(0.60-0.79)	4.2(1.1-15.8)	0.22(0.16-0.32)	18(4-86)	0.90(0.87-0.93)

(OR: odds ratio; Sens: sensitivity; Spec: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio; AUC: area under the curve).

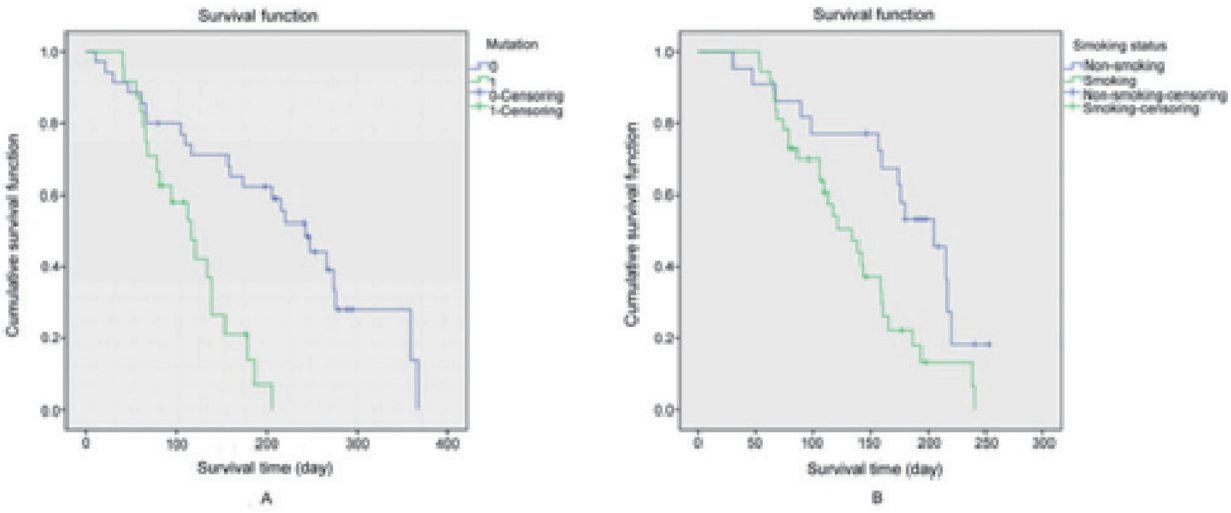

Figure 3. Kaplan-Meier curves of NSCLC patients treated by icotinib hydrochloride. ***(A)*** EGFR mutation, wild type and unknown status, 0 represents EGFR mutation group, 1 represents wild-type and unknown group; ***(B)*** Smoking and non-smoking status.

Table II. Subgroups' analysis results.

Group	PD	SD	PR+CR	ORR	Six-month DCR
Experiment group	21	21	18	18 (30.00%)	39 (65.00%)
Control group	26	19	15	15 (25.00%)*	34 (56.70%)#

Note: *indicates that in comparison of ORR, χ^2 = 0.376, p=0.540; #indicates that in the comparison of ORR between two groups, χ^2 =0.874, p = 0.350. (ORR: objective response rate)

Table III. Characteristics and efficacy of advanced NSCLC patients treated by icotinib hydrochloride.

Variables	Grouping	Cases	ORR/%	*p*	DCR/%	*p*
Sex	Male	37	11 (29.73%)	0.017	26 (70.27%)	0.137
	Female	23	14 (60.87%)		20 (88.92%)	
Age	<65	42	12 (28.57%)	0.232	32 (76.19%)	0.894
	≥65	18	8 (44.44%)		14 (77.78%)	
PS	0-1min	36	17 (47.22%)	0.457	29 (80.56)%	0.383
	≥2min	24	9 (37.50%)		17 (70.83%)	
Smoking status	Yes	33	10 (30.30%)	0.157	24 (72.73%)	0.119
	No	27	13 (48.15%)		24 (77.78%)	
Pathological type	Adenocarcinoma	43	15 (34.88%)	0.685	32 (74.42%)	0.242
	Non-adenocarcinoma	17	5 (29.41%)		15 (88.24%)	
Treatment	Second-line therapy	40	21 (52.50%)	0.043	32 (80.00%)	0.017
	Third-line therapy or above	20	5 (25.00%)		10 (50.00%)	
First-line therapy	CR/PR/SD	44	21 (47.73%)	0.043	36 (81.82%)	0.559
	PD	16	3 (18.75%)		12 (75.00%)	
Erythra	Yes	29	17 (58.62%)	0.021	27 (93.10%)	
	No	31	9 (30.00%)		19 (61.29%)	0.004
EGFR mutation	Mutant	24	16 (66.67%)			
	Wild type Unknown	8	1 (12.50%)	0.011	23 (95.83%)	0.002
		28	10 (35.71%)		3 (37.50%)	
					20 (71.42%)	
Mutant site	19del	15	10 (66.67%)	0.873	15 (100%)	
	21L858R	11	7 (63.63%)		10 (90.91%)	0.234
Brain metastases	Yes	36	9 (25.00%)	0.174	36 (100.00%)	
	No	24	10 (41.67%)		16 (66.67%)	0.000

Table IV. Analysis on median PFS and its correlative factors.

Characteristics		Median PFS (95%CI)	p
EGFR mutant status	Mutant	195 (73.25-288.12)	0.001
	Wild type and unknown	88 (11.63-157.53)	
Smoking status	Yes	134 (106.57-161.43)	
	No	205 (123.09-318.91)	0.008

their differences were statistically significant; differences between smoking patients and non-smoking patients were statistically significant (Table IV and Figure 3).

Adverse Reactions

There were respectively 2 cases and 7 cases of stage III and above had diarrhea respectively in icotinib group and erlotinib group, with statistical differences; 15 cases and 17 cases of stage I-II had erythra respectively in two groups without statistical significance; 2 cases and 1 case of stage III-IV had erythra respectively in two groups without statistical differences; 8 cases and 10 cases had nausea and vomiting respectively in two groups without statistical differences; 6 cases and 5 cases had liver function damage respectively in two groups without statistical differences.

Discussion

According to 2012 Chinese Cancer Registration Report[10], lung cancer has become the most common malignant tumor in China with high occurrence and mortality and bad prognosis, and the most of the patients are in advanced phase at the first diagnosis[11]. The treatment efficacy of chemo-radiotherapy for NSCLC has become into a bottleneck and the median survival time of advanced NSCLC patients still cannot be largely extended after chemo-radiotherapy. Therefore, it has become the inexorable trend to look for target drugs with high efficiency and low toxicity. Over these years, the appearance of gefitinib and erlotinib have un-curtained a new window for treatment of NSCLC. Chinese new NSCLC cases, however, more than 500,000 but less than 30,000 of them have accessed to these drugs. Icotinib hydrochloride was the first independently-developed, potent and novel targeted antineoplastic drug in China. Although icotinib hydrochloride is similar to gefitinib and erlotinib in chemical structure and working mechanism, it has better lipid solubility and easier to penetrate the cell membrane and blood-brain barrier; besides, it has advantages over efficacy, adverse reactions and treatment cost, which is more suitable for Chinese patients.

EGFR is a multi-function transmembrane glycoprotein correlated to cell proliferation, differentiation, adhesiveness, migration, invasiveness and its abnormal activation are closely related to the occurrence and progress of tumor. Icotinib hydrochloride is an oral EGFR-TKI which can selectively and competitively combine with EGFR-TK catalytic domain at ATP binding sites, interrupt the transmission of intracellular signal transduction, thereby inhibit the growth of tumor cells[12]. A clinical trial of stage III, ICOGEN, was performed to evaluate the efficacy and the safety of icotinib and gefitinib[8], and suggested that the median PFS was 4.6 months, ORR was 27.6% and DCR was 75.4% in icotinib group; ORR and DCR in control group were 27.2% and 74.9%, indicated that these two groups were similar in terms of treatment efficacy and safety. Anyway, in the icotinib group, the general occurrence of an adverse reaction related to drugs was 60%, the occurrence of erythra was 40% and the occurrence of diarrhea was 18.5%, which were all lower than those in gefitinib group. In an interesting research[5], ORR of the second-line therapy treated by gefitinib was 9.7%. The above two researches, however, focused on the Western population, and the ORR was over 30% only in subgroup analysis. In Lee et al research[13], randomly selected subjects were recruited to compare the efficacy of gefitinib and docetaxel in the second-line therapy, in which Asians were observed. Results showed that gefitinib was better than chemotherapy in efficacy. There were many small-sample trails while comparing the efficacy and adverse reaction to treatment by icotinib and erlotinib. Huang[14] recruited patients with NSCLC and failure in chemotherapy to analyze the efficacy and adverse reaction of patients who were treated respectively with icotinib and erlotinib (each including 13 cases) only to find that when using icotinib, the ORR and DCR were 23.1% and 61.6%. While using erlotinib, ORR and DCR were 15.4% and 69.2%, respectively, indicated no statistical differences, neither did statistical differences exist in adverse reactions such as erythra and nausea, vomiting, diarrhea. In this study, ORR and six-month DCR were respectively 30.00% and 65.00% in the icotinib group and 25.00% and 56.70% respectively in the erlotinib group, with no statistical difference. This investi-

gation indicated that icotinib hydrochloride was more efficient in treating advanced NSCLC to some extent. In this study, the median PFS of the experimental group (icotinib group) was 179 days (95% CI: 103.21-254.78) while that of the control group (erlotinib group) was 121 days (95% CI: 95.05-146.94). PFS of icotinib hydrochloride in this study was better than that (137 days) in ICOGEN research[8] since some patients received radiotherapy and chemotherapy, and the studying sample was relatively smaller with subjective selection preference. Moreover, it has been found that the patients under 65 years old and without smoking history and lower ECOG PS score had longer PFS.

There was a report in China that ORR of TKIs in treating advanced NSCLC was 15-59%[15]. In this work, most subjects were adenocarcinoma and patients with clear mutation accounts for a high percentage, 40%. Different subjects had influenced study results. Among 24 cases of patients with the sensitive mutation, 15 cases were deletion mutations of parkin gene at exons 19 and the other 11 cases were L858R point mutation at exons 21, and the two groups had similar ORR, where were 66.70% and 63.60%. In the IPASS research[16], ORR of gefitinib on patients without mutation of parkin gene at exons 19 was 84.8%, and 60.9% for patients with an L858R point mutation.

Concerning the treatment time, this report showed that efficacy of icotinib hydrochloride in the second-line therapy was better than that in the third-line therapy according to ORR (52.50% *vs.* 25.00%, p= 0.043) and DCR (80.00% *vs.* 50.00%, p=0.017). In comparison with the patients whose condition were not controlled through the first-line therapy, patients whose condition were under control had a better efficacy when they received the follow-up icotinib hydrochloride treatment. Gandara et al[17] suggested that ERCC1 level was low in patients with tumor caused by EGFR sensitive mutation, signified that they were more sensitive to platinum. It has been shown that ORR of the first-line therapy for patients with EGFR mutation was 47.3% and, in wild-type patients, was only 23.5%[18]. Several major experiments[19-21] demonstrated that the efficacy and PFS of patients with EGFR sensitive mutation and treated by TKI treatment in the first-line therapy were both better than those treated by chemotherapy. Currently, there was no prospective experiment, which compared TKI treatment in the first-line therapy and the second or third-line therapy in patients with EGFR gene mutation. In ICOGEN research[7], ORR of icotinib hydrochloride treatment in EGFR mutation group was 59%, but that in wild-type group was only 5.1%. In this study, there was a statistical difference between EGFR mutation group and wild-type group in ORR and DCR, among which ORR of EGFR mutation group was similar to the results of ICOGEN. Similar to the efficacy of first-line therapy in mutation group[18], icotinib showed significant efficacy in the treatment-experienced patient with the sensitive mutation.

After icotinib was applied in Chinese clinics, relative data[2] showed that for patients with unknown EGFR mutation, ORR was 34.5% and DCR was 79.4%; for patients with EGFR gene mutation, ORR was 54.1% and DCR was 93.5%. We focused on the efficacy of icotinib hydrochloride on NSCLC in the study, which indicated that as to the patients with unknown EGFR mutation, ORR was 35.71% and DCR was 71.42%. As to the patients with EGFR gene mutation, ORR was 66.67% and DCR was 95.83%, higher than those of wild-type patients. EGFR mutation was an influential factor of PFS, and the PFS of mutation patients was longer than that of wild-type patients. These results indicated that EGFR mutant status was a beneficial factor for PFS extension and icotinib showed positive outcomes on patients with unknown EGFR mutation. For patients with and without unknown EGFR mutation, the median PFR was 88 days (95% CI: 11.63-157.53 days), longer than that of patients treated only with chemotherapy[22]. PSF was not related to sex, age, PS score, pathological type, second or third-line therapy, the efficacy of the first-line therapy, erythra, mutant site and whether having brain metastases (p>0.05), but related to EGFR gene mutation and smoking status. Median PSFs were 195 days (95% CI: 73.25-288.12) in EGFR mutant group and 88 days (95% CI: 11.63-157.53) in wild-type group and unknown group, and their differences were statistically significant (p<0.05); differences between smoking patient and non-smoking patient were statistically significant (p<0.05). Many clinical researches[6,7,23,24] demonstrated that female and non-smoking Asian patients with adenocarcinoma were the dominant crowd of EGFR-TKI.

The adverse reactions mainly were erythra and diarrhea, and the most were light or moderate adverse reaction, which did not have to be treated specifically. There was no toxicity caused by the traditional chemotherapeutics such as myelosuppression. Moreover, the patients in the icotinib group had less erythra and diarrhea than in the gefitinib group.

Conclusions

As to the advanced NSCLC patients, icotinib, as an efficient anti-tumor and safe molecular targeted drugs, is worthy of further popularization and application. Furthermore, the popularity of EGFR mutation examination, as well as the maturity of EGFR-TKI first-line therapy and combination of chemotherapy with radiotherapy, allows more specific and efficient treatment mode for advanced NSCLC patients.

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Conflict of interest

The authors declare no conflicts of interest.

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