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Original Article

First-line icotinib versus pemetrexed plus cisplatin on quality of life and safety in elderly patients with EGFR-mutated advanced lung adenocarcinoma

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Abstract: Objective: To investigate the effect of first-line icotinib versus pemetrexed plus cisplatin on the quality of life and safety for elderly patients with epidermal growth factor receptor (EGFR)-mutated advanced lung adenocarcinoma. Methods: Ninety-eight elderly patients diagnosed with EGFR-mutated advanced lung adenocarcinoma by amplification refractory mutation system (ARMS) were randomly divided into an observation group and a control group, 49 cases in each. Patients in the observation group were given icotinib (125 mg of icotinib was taken orally three times a day, with a 4-week cycle), while in the control group were given pemetrexed plus cisplatin as first-line treatment (pemetrexed 500 mg/m^2, 3 weeks as a cycle, intravenous drip for 4 cycles, combined with cisplatin 25 mg/m^2 of corresponding dose). The objective response rate (ORR), disease control rate (DCR), incidence rate of adverse reactions and Short Form-36 (SF-36) score of quality of life were compared between the two groups after treatment. Results: The ORR of patients in the observation group was significantly higher than that in the control group (69.39% vs. 46.94%; P = 0.024). DCR in the observation group was significantly higher than that in the control group (91.84% vs. 75.51%; P = 0.029). After treatment, the SF-36 score of quality of life in the observation group was higher than that in the control group, with no statistically significant difference (P > 0.05). The score in both groups was significantly increased after treatment, with statistically significant differences (P < 0.05). Adverse reactions in the observation group were mainly skin rash (22.45%), diarrhea (18.37%), abnormal liver function (12.24%) and skin dryness and pruritus (4.08%), among which the incidence of skin rash, diarrhea and skin dryness and pruritus was higher than that in the control group (P = 0.000, P = 0.002, P = 0.558, respectively). Whereas, the main adverse reactions in the control group were neutropenia (71.43%), anemia (67.35%), leukopenia (57.14%), abnormal liver function (40.82%) and nausea and vomiting (20.41%), and the incidence of these five adverse reactions in the control group was higher than that in the observation group (P = 0.000, P = 0.000, P = 0.000, P = 0.001, P = 0.004, respectively). The median progression-free survival (mPFS) in the observation group was higher than that in the control group (P = 0.003). Conclusion: Icotinib for the first-line treatment of elderly patients with EGFR-mutated advanced lung adenocarcinoma has the advantages of high safety, increasing the ORR and DCR, improving the quality of life, reducing the incidence of adverse reactions and prolonging the survival time; all of which brings greater clinical benefits to patients.

Keywords: Icotinib, epidermal growth factor receptor, lung adenocarcinoma, quality of life, safety

Introduction

Lung cancer is a major malignant tumor that endangers human health: among which non-small cell lung cancer (NSCLC) is the most common type, accounting for about 80%-85%, and lung adenocarcinoma accounts for about 50%; and the elderly, especially those aged over 70 years, are predominant affected [1, 2]. Most patients have already missed the best surgical period at their first diagnosis. Pemetrexed, a multi-target anti-folic acid drug, effectively inhibits thymidylate synthase (TS) and dihydrofolate reductase (DHFR) required for purine and pyrimidine synthesis by conversion into polyglutamic acid compounds, thus inhibiting the growth of tumor cells [3-5]. Platinum drugs combined with chemotherapy drugs such as pemetrexed are currently important treatment methods for advanced NSCLC, and they are also widely used in clinical application of advanced lung adenocarcinoma with epidermal

Table 1. General information

	Observation group (n, %)		Control group (n, %)		χ^2	P
	n	%	n	%		
Age (year)					0.373	0.541
< 75	29	59.18	26	53.06		
≥ 75	20	40.82	23	46.94		
Gender					0.169	0.681
Male	19	38.78	21	42.86		
Female	30	61.22	28	57.14		
Clinical stage					0.043	0.835
III	18	36.73	19	38.78		
IV	31	63.27	30	61.22		
Smoking history					0.883	0.347
Yes	10	20.41	14	28.57		
No	39	79.59	35	71.43		
Lung adenocarcinoma History					0.460	0.498
Yes	12	24.49	15	30.61		
No	37	75.51	34	69.39		
ECOG score					0.186	0.667
0-2	34	69.39	32	65.31		
3-4	15	30.61	17	34.69		

Note: ECOG, Eastern Cooperative Oncology Group.

growth factor receptor (EGFR) gene mutation [6, 7]. One study has shown that this combination therapy achieved good efficacy in first-line treatment of stage IV NSCLC, with an objective response rate (ORR) of 30.6% and a median progression-free survival (mPFS) of 4.8 months; but some studies have shown that its incidence of adverse events is relatively high [8-10]. However, in recent years, EGFR-tyrosine kinase inhibitor (EGFR-TKI), an effective targeted drug for the treatment of advanced lung adenocarcinoma, has attracted much attention from relevant researchers [11-13]. Icotinib is a new type of oral targeting drug independently developed in China. Compared with other clinically common EGFR-TKI drugs such as erlotinib and gefitinib, it has a similar therapeutic effect but higher safety and a more favorable price [14]. At present, research on icotinib as a second-line treatment of advanced NSCLC is greater than that for a first-line treatment. Therefore, in this paper, 98 elderly patients with EGFR-mutated lung adenocarcinoma admitted to Chun'an First People's Hospital were taken as research subjects to explore the effect of first-line treatment with icotinib, pemetrexed and cisplatin on safety and quality of life in patients. The reports were as follows.

Materials and methods

Research data

From May 2015 to May 2018, 98 elderly patients with advanced lung adenocarcinoma (stage III-IV) were selected, aged 60-88 years old, including 40 males and 58 females, with a sex ratio of 1:1.45. The patients were randomly divided into an observation group and a control group, with 49 cases in each group. Inclusion criteria: all patients were diagnosed with EGRF-mutated lung adenocarcinoma by DNA sequencing and related pathology, and staging was performed according to TNM staging criteria of the International Association for the Study of Lung Cancer (IASLC) in 2009; patients with normal liver, renal function and blood routine; all patients voluntarily participated and signed informed consent forms. Exclusion criteria: patients with hematological diseases or coagulation abnormalities; patients with a recent history of using related targeted drugs; patients with severe heart, lung, liver and kidney dysfunctions; patients allergic to the drugs in this study. This study was approved by the Ethics Committee of Chun'an First People's Hospital and met the requirements of medical ethics.

Research methods

The patients in the observation group were treated with icotinib: icotinib (commodity: Conmana, Zhejiang Betta Pharmaceutical Co., Ltd.) 125 mg/tablet was taken orally three times a day, with a 4-week cycle, until the disease progresses. Patients in the control group were treated with pemetrexed (commodity: Alimta, Lilly France S.A.S) combined with cisplatin (commodity: Cisplatin Injection, Hospira Australia Pty Ltd.) for first-line treatment, one cycle for 3 weeks and repeated for 4 cycles: patients were given pemetrexed (500 mg/m^2) intravenously on the first day of the first cycle, and then cisplatin (25 mg/m^2) of the corresponding dose was injected intravenously.

Table 2. Comparison of curative effect between the two groups (n, %)

Group	CR	PR	SD	PD	ORR	DCR
Observation group (n = 49)	2 (4.08)	32 (65.31)	11 (22.45)	4 (8.16)	34 (69.39)	45 (91.84)
Control group (n = 49)	0 (0.00)	23 (46.94)	14 (28.57)	12 (24.49)	23 (46.94)	37 (75.51)
χ^2	2.042	3.356	0.483	4.780	5.074	4.780
P	0.153	0.067	0.487	0.029	0.024	0.029

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table 3. SF-36 score of quality of life before treatment between the two groups

	Observation group (n = 49)	Control group (n = 49)	t	P
Physiological functioning	63.03 ± 5.72	62.11 ± 4.42	4.122	0.105
Role-physical	59.82 ± 5.37	59.95 ± 4.67	5.194	0.152
Bodily pain	52.11 ± 5.52	51.24 ± 5.63	4.531	0.513
General health	62.13 ± 5.25	62.45 ± 5.36	5.044	0.302
Vitality	61.53 ± 4.39	60.41 ± 4.57	5.885	0.462
Social functioning	60.84 ± 5.55	61.92 ± 4.79	5.409	0.632
Role-emotional	62.85 ± 5.63	62.20 ± 5.42	5.061	0.402
Mental health	61.79 ± 4.49	61.82 ± 4.65	5.323	0.136

Note: SF-36, Short Form-36.

Table 4. SF-36 score of quality of life after treatment between the two groups

	Observation group (n = 49)	Control group (n = 49)	t	P
Physiological functioning	76.13 ± 6.23[a]	67.25 ± 3.96[b]	7.429	0.213
Role-physical	79.62 ± 4.77[a]	70.12 ± 4.03[b]	6.022	0.367
Bodily pain	75.13 ± 4.63[a]	62.04 ± 6.24[b]	7.564	0.626
General health	80.52 ± 6.13[a]	69.85 ± 5.17[b]	7.143	0.598
Vitality	72.65 ± 4.34[a]	66.91 ± 3.86[b]	5.309	0.435
Social functioning	78.61 ± 5.62[a]	72.12 ± 4.75[b]	4.416	0.411
Role-emotional	81.82 ± 6.72[a]	62.20 ± 5.42[b]	7.603	0.501
Mental health	83.78 ± 6.42[a]	70.11 ± 5.46[b]	5.825	0.216

Note: Compared with before treatment in observation group, [a]$P < 0.05$; compared with before treatment in control group, [b]$P < 0.05$. SF-36, Short Form-36.

Efficacy evaluation

Efficacy evaluation was conducted according to the *Response Evaluation Criteria in Solid Tumors (RECIST1.1 version)* [15]. Complete response (CR): all target lesions of the patient disappeared and improvement lasted for more than 4 weeks. Partial response (PR): the sum of the maximum diameters of the baseline lesions was reduced by ≥ 30% compared with before treatment. Stable disease (SD): the sum of the diameter of the lesion decreased but more than PR, or the sum of the maximum diameter of the lesion slightly increased but less than progressive disease (PD). PD: new lesions occurred or the sum of the maximum diameters of all lesions increased by more than 20%. Objective response rate (ORR) = CR + PR (%), disease control rate (DCR) = CR + PR + SD (%).

Outcome measures

Main outcome measures: quality of life was assessed by Short Form-36 (SF-36) scale, which included 36 questions and 8 dimensions: physiological functioning, physical role, body pain, general health, vitality, social functioning, emotional role and mental health [16]. The quality of life was positively related to the score.

Adverse reactions: according to the adverse reaction rating standard established by US National Cancer Institute, the toxic side effects were evaluated and classified into 0-4 grades.

Secondary outcome measures: PFS, which refers to the time from the patient's first medication to disease progression or death from any cause. PFS of patients was obtained through outpatient or telephone follow-up two years later.

The physical condition of the patients was scored according to the grading standards established by the Eastern Cooperative Oncology Group (ECOG) of the United States.

Statistical methods

SPSS 20.0 software was used to analyze the data. The enumeration data were analyzed wi-

Table 5. SF-36 score of quality of life before and after treatment between the two groups

	Observation group (n = 49)	Control group (n = 49)	t	P
Physiological functioning	13.10 ± 6.23	5.14 ± 0.46	4.415	0.113
Role-physical	19.80 ± 4.77	10.17 ± 0.64	3.241	0.236
Bodily pain	23.02 ± 4.63	10.80 ± 0.61	4.352	0.356
General health	18.39 ± 6.13	7.40 ± 0.19	6.301	0.215
Vitality	11.12 ± 4.34	6.5 ± 0.71	4.139	0.205
Social functioning	17.77 ± 5.62	10.20 ± 0.04	4.426	0.126
Role-emotional	18.97 ± 6.72	6.12 ± 0.02	5.061	0.332
Mental health	21.99 ± 1.93	8.29 ± 0.81	5.215	0.425

Note: SF-36, Short Form-36.

Table 6. Comparison of adverse reactions between the two groups (n, %)

	Observation group (n = 49)	Control group (n = 49)	χ^2	P
Abnormal liver function	6 (12.24)	20 (40.82)	10.261	0.001
Skin rash	11 (22.45)	0 (0.00)	12.391	0.000
Diarrhea	9 (18.37)	0 (0.00)	9.910	0.002
Neutropenia	1 (2.04)	35 (71.43)	50.756	0.000
Anemia	0 (0.00)	33 (67.35)	49.754	0.000
Leukopenia	0 (0.00)	28 (57.14)	39.200	0.000
Nausea and vomiting	1 (2.04)	10 (20.41)	8.295	0.004
Skin dryness and pruritus	2 (4.08)	1 (2.04)	0.344	0.558

th χ^2 test, and the measurement data were expressed by mean ± standard deviation ($\bar{x}$ ± sd). The comparison before and after treatment in the same group was conducted by paired t test, while the comparison between the two groups was conducted by t test. The survival analysis was performed by Log-rank test. When $P < 0.05$, the difference was statistically significant.

Results

General information

In this study, a total of 98 patients were enrolled. See **Table 1** for general data comparison. There was no significant difference between the two groups (both $P > 0.05$).

Comparison of curative effect

ORR in the observation group (69.39%) was significantly higher than that in the control group (46.94%) ($\chi^2 = 5.074$, $P = 0.024$). DCR in the observation group (91.84%) was significantly higher than that in the control group (75.51%) ($\chi^2 = 4.780$, $P = 0.029$), as shown in **Table 2**.

SF-36 score of quality of life before and after treatment

There was no significant difference in quality of life between the two groups before treatment (both $P > 0.05$). After treatment, the SF-36 score in the observation group was higher than that in the control group, but there was no significant difference between the two groups before and after treatment ($P > 0.05$). Paired t test found that the differences of all dimensions in SF-36 between the two groups before and after treatment were statistically significant ($P < 0.05$) (**Tables 3**-**5**).

Comparison of safety between the two groups

The main adverse reactions in the observation group were skin rash (22.45%), diarrhea (18.37%), abnormal liver function (12.24%) and skin dryness and pruritus (4.08%), with each proportion lower than 30%. The main adverse reactions in the control group were neutropenia (71.43%), anemia (67.35%), leukopenia (57.14%), abnormal liver function (40.82%) or nausea and vomiting (20.41%), among which the proportion of patients with single adverse reaction was as high as over 70%, see **Table 6**.

Comparison of PFS between the two groups

The mPFS of 49 patients in the observation group was 8.2 months, while that in the control group was 6.1 months. Therefore, the mPFS in the observation group was higher than that in the control group, with statistically significant difference ($\chi^2 = 8.828$, $P = 0.003$). See **Figure 1**.

Discussion

Clinically, about 30%-40% of lung adenocarcinoma patients have developed to advanced

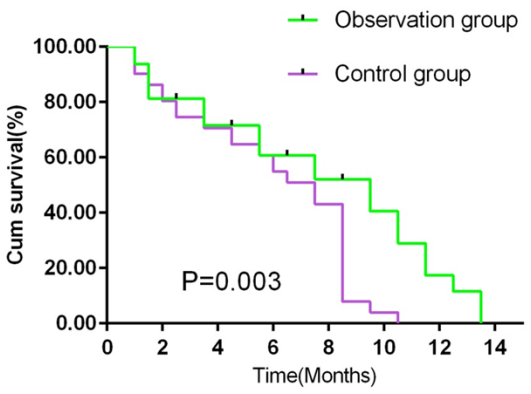

Figure 1. Comparison of PFS between the two groups. PFS, progression-free survival.

stages (IIIB-IV) when they are first diagnosed, and their quality of life was improved mainly through chemotherapy [17, 18]. Icotinib is an oral EGFR-TKI targeted drug independently developed in China, which is safer and more effective than antineoplastic drugs such as pemetrexed.

This study mainly compared the effect of icotinib and pemetrexed combined with cisplatin on the quality of life and safety in elderly patients with EGFR-mutated advanced lung adenocarcinoma. The results showed that the ORR in the observation group after treatment was 69.39%, significantly higher than that in the control group (46.94%), which is consistent with relevant reports [19, 20]. After treatment, the DCR in the observation group (91.84%) was significantly higher than that in the control group (75.51%), which is consistent with the research by Rong Biaoxue et al. [21]. After treatment, the SF-36 scores in all dimensions in the observation group were higher than those in the control group, without significant difference, which shows that icotinib is effective in the treatment of lung adenocarcinoma and clearly improves the quality of life of patients. The incidence of adverse reactions in the observation group was significantly lower than that in the control group, indicating the high safety of icotinib, which is similar to the research of other relevant scholars [22, 23]. The mPFS in the observation group was significantly higher than that in the control group.

To sum up, as the first-line treatment for elderly patients with EGFR-mutated advanced lung adenocarcinoma, icotinib has the advantages of high safety, increased treatment efficiency and DCR, improved quality of life, reduced incidence of adverse reactions and prolonged survival time of patients compared with pemetrexed plus cisplatin, which is worthy of clinical application. However, considering patient's drug tolerance, a larger sample size randomized study is still needed to further verify the clinical value of icotinib.

Disclosure of conflict of interest

None.

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