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ORIGINAL ARTICLE

The efficacy of Kanglaite injection during treatment with tyrosine kinase inhibitor in elderly patients with non-small cell lung cancer*

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Abstract

Objective Epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR–TKIs) are widely used in the treatment of EGFR mutation-positive non-small cell lung cancer (NSCLC) patients. The Kanglaite injection (KLT) is a novel broad-spectrum anti-cancer injection produced from traditional Chinese medicinal herbs (coix seed). After its approval in 1995, KLT has become the most popular anti-cancer drug in China. As of this writing, no standard treatment guideline is available for elder patients with NSCLC, and the role of traditional Chinese medicinal herbs, including KLT, combined with TKI treatment remains unknown. This retrospective study evaluated the efficacy and safety of KLT in elderly NSCLC patients during TKI treatment.

Methods Thirty elderly patients aged 71-79 years with histopathologically confirmed NSCLC attending the General Hospital of the Shenyang Military Region were enrolled in the study and received EGFR-TKI treatment. All participants received 200 mL KLT injections at the same time on days 1–21. Erlotinib (150 mg) or gefitinib (250 mg) was administered daily from days 1 to 21, and the cycle was repeated every 21 days. The endpoint of the primary study was the disease control rate.

Results Thirty elderly patients were enrolled in this study. The objective response rate was 21.3% [95% confidence interval (CI): 8.6% to 35.2%], whereas the disease control rate was 80.4% (95% CI: 71.8% to 97.0%). The grade 3 or 4 adverse effects included leucopenia (13.7%), neutropenia (13.4%), anemia (2.9%), and nausea or vomiting (2.7%).

Conclusion The administration of KLT combined with erlotinib or gefitinib showed high efficacy in elderly NSCLC patients. The adverse effects of the drug combination were well tolerated by the patients. KLT combined with TKI treatment might provide a satisfactory therapeutic strategy for elderly NSCLC patients.

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Key words: non-small cell lung cancer (NSCLC); Kanglaite injection (KLT); epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI)

Lung cancer is characterized by malignant tumors and has the highest morbidity and mortality rates worldwide. About 1.60 million new patients are diagnosed with lung cancer, and 1.38 million patients die of lung cancer each year. Non-small cell lung cancer (NSCLC) is a lung cancer with poor prognosis that is resistant to chemotherapy [1]. Molecular targeted therapy has been the main clinical treatment option; in epidermal growth factor receptor (EGFR) mutation-positive patients, EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib or gefitinib have shown a longer progression-free survival (PFS) and overall survival (OS) in NSCLC patients [2]. Recent studies have shown that TKI-based treatment combined with chemotherapy offers better clinical benefits. However, the used of combined treatment has been extremely limited in elderly patients due to poor tolerance and adverse reactions. Thus, identification of good therapeutic options that allow elderly patients to benefit from TKI-based treatment is of great clinical significance.

In recent years, traditional Chinese medicine has been

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widely used in China as an adjuvant treatment during chemotherapy and radiotherapy for cancer, offering good therapeutic effects [3]. Kanglaite injection (KLT) is a Chinese herbal compound that has been widely used for the treatment of non-small-cell lung, liver, and gastric cancer in China [4]. KLT has been administered to approximately 6 million patients with these cancers. The main ingredient of KLT is seed oil, which has been widely used for cancer treatment and has good therapeutic effects on cancer metastasis and immunological disorders [5]. Preclinical studies have found that KLT may block the tumor cell cycle at the G2/M phase and induce tumor cell apoptosis by up-regulating the expression of Fas/Apo-1 and down-regulating the expression of Bcl-2 and COX-2 [6–7]. KLT significantly decreases cancer cachexia, improves the quality of life of cancer patients, and may ameliorate multiple drug resistance in cancers when combined with radiotherapy and chemotherapy in clinical use.

Our study analyzed the effects and adverse reactions of TKI treatment combined with KLT injection in elderly patients with NSCLC. The results suggest that this combined treatment might provide a satisfactory therapeutic strategy for elderly NSCLC patients.

Materials and methods

Patients

Thirty-two elderly patients (71–79 years of age) with histopathologically confirmed NSCLC attending the General Hospital of Shenyang Military Region were enrolled in the study. All participants received continuous daily EGFR-TKI treatment and simultaneous KLT injections. Before treatment, these patients had Eastern Cooperative Oncology Group (ECOG) performance scores between 0–1 and no obvious abnormal blood, liver and kidney function, and electrocardiogram findings.

Treatment

All patients were administered oral erlotinib (150 mg) or gefitinib (250 mg) daily from days 1 to 21, and the cycle was repeated every 21 days. The KLT injection (200 mL) was also administered daily on days 1 to 21. The endpoint of the primary study was the disease control rate. If any patient could not tolerate the adverse reactions during treatment, the dosage was reduced by 20% in the next treatment cycle. The treatments were stopped if the patients still could not tolerate the adverse reactions. After two cycles of TKI combined with KLT treatment, the therapeutic effects were evaluated. The treatments were terminated if disease progression or intolerable adverse reactions occurred.

Assessments and statistical methods

Baseline tumor measurements were taken no more than one week before the start of treatment. According to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, tumor response was evaluated using the same imaging technique that was used at baseline. At the end of the treatment period, the best tumor response was recorded. Safety measures including adverse events, physical examinations, and clinical laboratory tests (hematology, blood biochemistry, hepatic functions, and renal functions) were assessed weekly. Toxicity was graded using version 2.0 of the National Cancer Institute Common Toxicity Criteria.

Statistical analysis was performed using PASW Statistics for Windows, Version 18.0. Differences among variables were assessed by two-tailed Student's *t*-tests. Data were presented as the means ± standard error of the mean unless otherwise indicated. $P<0.05$ was considered statistically significant.

Ethics statement

All patients were from China and received treatment in our hospital. All clinical investigations were approved by the General Hospital of Shenyang Military Region Ethical Committee and all patients involved in this study signed consent forms.

Results

Between June 2013 and March 2016, a total of 30 patients were enrolled in the study. The baseline patient characteristics were listed in Table 1. The median age was 75 years (range, 71–79) and there were 16 male and 14 female patients. All patients had a good performance status; 24 and 8 had ECOG performance status scores of 0 and 1, respectively. Sixteen patients had stage IIB tumors, while 14 patients had stage IV tumors. Twenty-nine patients had adenocarcinoma and one patient had large cell carcinoma. Among the 30 patients, 19 were treated with TKI in the first round, and 11 were treated in second or third rounds of treatment. Five patients achieved partial response (PR) and 21 had stable disease (SD); the objective response rate (ORR) was 16.7% and the disease control rate (DCR) was 86.7% in the 30 patients who received the combined EGFR-TKI and KLT treatment. All patients received at least two cycles of KLT plus TKI. At the end of the follow-up in March 2016, no patients were lost to follow-up, and the efficacy and adverse reaction were evaluated for patients.

In brief, of the 30 patients treated with KLT plus erlotinib/gefitinib, no complete response (CR) was observed; five patients (5/30, 16.7%) achieved PR, 21 patients (21/30, 70%) achieved SD, and four patients (4/30, 13.3%) had progressive disease (PD). The ORR [(CR+PR)/*n*] was 16.7% (5/30, 95% CI: 6.5-37.8%) and

Table 1 Patient characteristics (Total=30)

Characteristics of patients	*n*	%
Age (years, range)	75	71–79
Sex		
Male	16	53.3
Female	14	46.7
S (m^2, mean ± s)	1.83 ± 0.18	
Stage		
IIB	16	53.3
IV	14	46.7
ECOG Performance status		
0	22	73.3
1	8	26.7

Table 2 Response in elderly patients with NSCLC treated with EGFR-TKIs plus KLT (Total=30)

Response	*n*	%
CR	0	0
PR	5	16.7
SD	21	70.0
PD	4	13.3
ORR	16.7	
DCR	86.7	

Table 3 Toxicity in patients (*n*, %)

Toxicity	I/II	III/IV
Nausea/vomiting	2 (6.7)	1 (3.3)
ALT/AST	6 (20)	2 (6.7)
Rash	24 (80)	1 (3.3)
Pyrexia	2 (6.7)	0 (0)
Fatigue	9 (30)	0 (0)

the DCR [(CR+PR+SD)/n] was 86.7% (26/30, 95% CI: 70.2–97.0%). The tumor responses were summarized in Table 2.

Discussion

Several randomized phase III clinical trials of gemcitabine or paclitaxel plus platinum in combination with continuous daily administration of erlotinib or gefitinib as first-line therapy failed to show improved survival in patients with advanced NSCLC [8]. This led to the conclusion that chemotherapy combined with EGFR-TKI is not a good choice and there has been little interest in pursuing such strategies. However, a later randomized phase III study showed significant improvements in progression-free and overall survival in patients with advanced pancreatic cancer receiving continuous daily erlotinib in addition to gemcitabine compared with gemcitabine alone [9]. The current study assessed the efficacy and safety of KLT combined with the continuous daily administration of erlotinib or gefitinib in progressive NSCLC patients during TKI-based treatment. The results showed that the treatment modality was effective and safe in those patients. Out of 30 patients, five and 21 achieved PR and SD, respectively. The grade 3 and 4 adverse events included nausea/vomiting (3.3%), abnormal liver function(6.7%), and rash (3.3%). And the toxicity of patients were summarized in Table 3. In that study, the DCR and ORR were 77.8% and 25.9%, respectively. The adverse events were also well tolerated by patients. These results showed that compared with TKI treatment for NSCLC, the patients in the current study showed better ORR and DCR and the adverse events were well tolerated with combined treatment; moreover, KLT combined with erlotinib/gefitinib may offer better efficiency than EGFR-TKI for the treatment of NSCLC.

Preclinical studies have shown that TKI influences the expression and activity of thymidylate synthase in tumor cells, which increases the killing effect of pemetrexed [10]. Studies also found that KLT may block the tumor cell cycle at the G2/M phase and induce tumor cell apoptosis by up-regulating the expression of Fas/Apo-1 and down-regulating the expression of Bcl-2 and COX-2. KLT also has been found to significantly decrease cancer cachexy and improve the quality of life of cancer patients, which might enhance the TKIs efficiency. However, more basic research is needed to explain the mechanism by which KLT in combination with TKI offers better efficacy in NSCLC patients.

In conclusion, our study showed that KLT combined with continuous TKI treatment offered better efficacy and tolerability in patients with progressive NSCLC patient during TKIs treatment. The study suggested that KLT combined with TKI treatment might be a good strategy in progressive NSCLC patients.

Competing interests

We declare no conflicts of interests.

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