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RESEARCH ARTICLE

TEYSUNO™ (S-1) IS BENEFICIAL FOR EGFR-TKI REFRACTORY NSCLC PATIENTS

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Abstract

This study is to explore Teysono™ (S-1), an oral fixed-dose combination of three active substances, in the treatment of Non-small-cell lung carcinoma. Twenty-four patients with advanced NSCLC were recruited and were treated with salvage therapy with orally administered Teysono capsules. Treatment was followed by one week of rest before the second cycle. The response and side effects are observed after two cycles of therapy. Two patients showed partial response, ten showed stable disease, twelve showed progressive disease and none showed complete response. The objective response rate was 8.3% and the disease control rate was 50.0%. Disease control rate and progression-free survival were higher in patients who had previously received at least six months of EGFR-TKI therapy. All side effects were considered tolerable, and no fatalities were associated with the therapy. In conclusion: Teysono is an effective treatment strategy for EGFR-TKI refractory NSCLC patients, providing a novel therapeutic option for these patients.

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Introduction:-

Lung cancer is the leading cause of cancer-related global deaths with a five-year survival rate of 17% (1-3). More than 80% of lung cancer cases are classified as non-small-cell lung carcinoma (NSCLC) (4). At diagnosis, almost 65% NSCLC patients already have advanced disease, and can not be properly treated by surgery (5). Despite recent progress, standard therapy with platinum based chemotherapy agents results in median survival of only ten months (6), underscoring the need for novel targeted therapies for NSCLC patients.

The tyrosine kinase receptor EGFR (epidermal growth factor receptor) is often overexpressed or mutated in NSCLC, making it an attractive target for therapy (7). However, while most patients initially respond well to EGFR tyrosine kinase inhibitors (EGFR-TKIs), they ultimately develop resistance to therapy within 6 -12 months (8, 9). Therefore, it is necessary to develop therapeutic strategies for patients with EGFR-TKI resistant NSCLC, however few effective agents are available.

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Teysuno™ (S-1) is an oral fixed-dose combination of three active substances including tegafur, gimeracil, and oteracil (10). After absorption, tegafur is converted into 5-FU, and its degradation is inhibited the dihydropyrimidine dehydrogenase (DPD) inhibitor (Gimeracil). Meanwhile, the orotate phosphoribosyltransferase (OPRT) inhibitor (Oteracil) is used to decrease the activity of 5-FU in the gut in order to minimize toxicity to the normal gastrointestinal (GI) mucosa (11). Teysuno has been approved for the treatment of patients with advanced gastric cancer (12), however its clinical value in treating lung cancer, particularly EGFR-TKI refractory NSCLC, is unknown. Given the therapeutic benefits of Teysuno™ (S-1) for gastric cancer patients, we hypothesized that it might also be effective for EGFR-TKI refractory NSCLC patients. To test this hypothesis, we treated NSCLC patients with Teysuno and observed an objective response rate (ORR) of 8.3% (2/24) and the disease control rate (DCR) of 50.0% (12/24). Furthermore, the quality of life was significantly improved after Teysuno treatment with tolerable side effects.

Materials and methods:-

Patients:-

All 24 advanced NSCLC patients were recruited between March 2007 and May 2014 at the first and second affiliated Hospital of Harbin Medical University. All of these patients were resistant to, or failed to respond to the first line platinum-based chemotherapy and subsequent Erlotinib or Gefitinib treatment. In detail, all patients had to meet the following inclusion criteria: (1) first-line platinum-containing chemotherapy as a standard two-drug program; (2) The clear and objective diagnosis of pathological NSCLC lesions; (3) ECOG physical condition Rating ≤ 2 points; (4) the estimated survival time > 3 months; (5) normal bone marrow, liver and kidney function; (6) patients with multiple intra-thoracic or distant metastasis. This study was approved by the Ethics Committee and all patients agreed to participate in this study and provided a signed informed consent form.

Methods:-

The information regarding gender, age, histological type, clinical stage, smoking history, PS score and previous therapy history were obtained from the patient's medical records or follow-up information obtained upon registration or by telephone call. Patient response was defined using RECIST criteria as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Objective response rate (ORR) was calculated from the percentage of CR and PR. The disease control rate (DCR) was calculated from percentage of CR, PR, and SD. Progression-free survival (PFS) was measured based on the length of time during and after treatment without disease progression. Patient quality of life was guided by the Karnofsky score, with a decreasing score (< 10) indicating declining quality of life, and an increasing score (> 10) indicating improvement. The side effects were measured according to the third version of Common Terminology Criteria for Adverse Events (CTCAE) created by NCI.

Treatment:-

All 24 patients were treated with salvage therapy. Patients were orally administered 80mg/mL of Teysuno capsules twice a day for 14 days (S-1, Dapeng Pharmaceutical Co.), followed by seven days of rest. The response and side effects are observed after two cycle's treatment.

Statistics:-

Statistical analysis was performed using SPSS 15.0 (SPSS INC, Chicago IL, USA). The survival rates were analyzed by Kaplan-Meier method. The $P < 0.05$ was considered statistically significant.

Results:-

Short-term efficacy of Teysuno™ (S-1) salvage therapy in EGFR-TKI refractory NSCLC patients:-

We recruited 24 EGFR-TKI refractory NSCLC patients for Teysuno™ (S-1) therapy to assess the therapies short-term efficacy in all patients. The general characteristics of the patients before treatment are described in Table 1. There were 13 male and 11 female patients, with a median age of 55 years and a range from 34 to 72 years. Patients were grouped into disease stages based on the 2009 International Association for the Study of Lung Cancer staging system.

Table 1:- The general baseline information of 24 recruited advanced NSCLC patients.

General characteristics	Cases number	Percentage (%)
Gender		
male	13	54.1
female	11	45.8
PS score		
0-1	11	45.8
2	13	54.1
Pathologic type		
Adenocarcinoma	14	58.3
Squamous	6	25.0
Unclassified	4	16.7
Smoking history		
Smoking	14	58.3
Never smoking	10	41.7
Drug history		
Gefitinib	14	58.3
Erlotinib	10	41.7
TKI treatment time		
≥ 6 months	9	37.5
< 6 months	15	62.5
Number of metastases		
1	3	12.5
2	15	62.5
≥ 3	6	25
Organ metastasis		
Brain	7	
lung	17	
liver	5	
Pleural effusion	7	
bone	12	
Adrenal metastasis	6	

After the completion of the Teysuno therapy regimen, two patients showed partial response (PR), ten patients showed stable disease, twelve patients showed progressive disease and no patient showed complete response. The objective response rate (ORR) was 8.3% (2/24) and the disease control rate (DCR) was 50.0% (12/24). Further analysis showed that the DCR in patients with at least 6 months EGFR-TKI treatment is significantly higher than that of patients with less than 6 months of EGFR-TKI treatment ($P = 0.035$). PS score and gender were not associated with ORR or DCR in our cohort ($P > 0.05$, Table 2).

Table 2:- Analysis of Teysuno associated factors

Factors	case	PR	SD	PD	ORR (%)	X^2 (p)	DCR (%)	X^2 (p)
Gender								
male	13	1	6	6	7.7	0.015	53.8	0.168
female	11	1	4	6	9.1	0.902	45.5	0.682
PS score								
0-1	11	1	6	4	9.1	0.015	63.6	1.510
2	13	1	4	8	7.69	0.902	38.5	0.219
TKI duration								
≥ 6 months	9	1	6	2	11.1	0.145	77.8	4.44
< 6 months	15	1	4	10	6.67	0.703	33.3	0.035
metastasis								
≥ 3	6	1	3	2	66.7	0.727	66.7	0.889
< 3	18	1	7	10	44.4	0.394	44.4	0.346

PFS in Teysuno™ (S-1) salvage therapy and its associated factors:-

The median follow-up time for all patients was 5.5 months (range: 2.0 – 15 months). The median progression-free survival (PFS) for all patients was 5.042 ± 0.633 months (Figure 1A). The PFS in patients who received at least 6 months of EGFR-TKI treatment (7.0 ± 1.064 months; from 4.908 to 9.092 months) is significantly longer than that of patients with less than 6 months of EGFR-TKI treatment (3.876 ± 0.631 months; from 2.639 to 5.104 months) ($X^2 = 4.246$; $P = 0.039$) (Figure 1B). Gender and metastatic load had no relationship on PFS. We used Cox analysis to determine which patient factors contributed to the effects of Teysuno salvage therapy. However, we did not identify any relation between any of our analyzed factors (gender, PS score, the number of metastasis, bone metastasis, brain metastasis and lung metastasis) and therapeutic efficacy.

Quality of life before and after Teysuno™ (S-1) salvage therapy:-

Overall, patient quality of life was significantly improved after Teysuno treatment. The mean body weight after therapy was 58.67 ± 7.574 , which was significantly higher than it before treatment (57.54 ± 6.393 Kg) ($t = 2.086$, $p = 0.048$) (Table 3). Based on Karnofsky score, 58.3% (14/24) patients had improved quality of life, 25.0% (6/24) of patients were stable, and 16.7% (4/24) of patients had a lower quality of life after Teysuno therapy. The KPS score after treatment (56.67 ± 9.631) is also significantly increased compared to the score before treatment (52.92 ± 6.24) (Table 4). Furthermore, disease symptoms including hemoptysis, cough, dyspnea, chest pain and other symptoms were significantly reduced after treatment. Taken together, our finding showed that NSCLC patient quality of life is significantly improved by Teysuno therapy.

Table 3:- Body weight before and after Teysuno treatment

	Before treatment	After treatment
case	24	24
body weight (M±S)	57.54 ± 6.393	58.67 ± 7.574
T	2.086	
P	0.048	

Table 4:- KPS score before and after Teysuno treatment

	Before treatment	After treatment
case	24	24
KPS score (m±s)	52.92 ± 6.241	56.67 ± 9.631
T	2.387	
P	0.026	

Side effect of Teysuno™ (S-1) salvage therapy:-

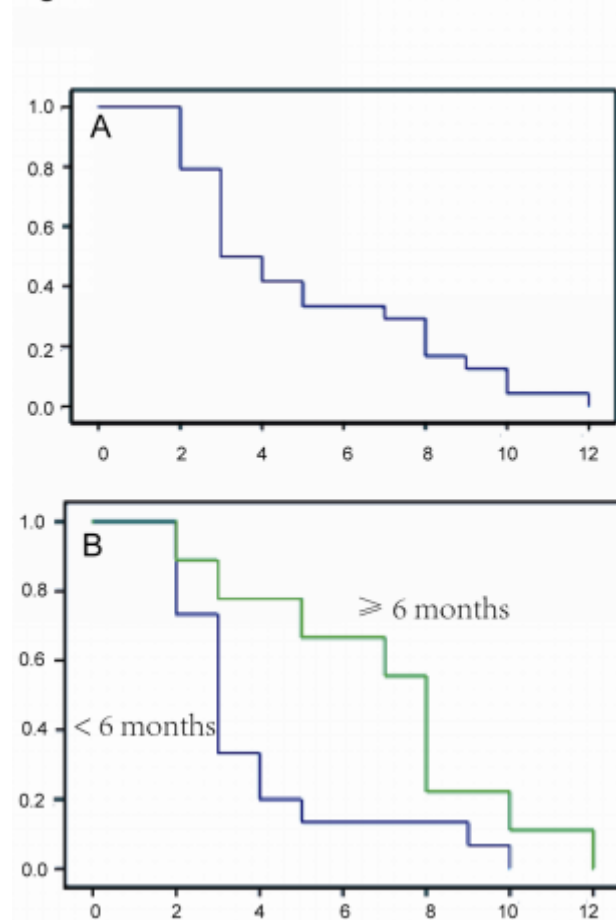
Information regarding the side effects was obtained from all patients (Table 5). The side effects include nail changes, skin pigmentation, anorexia, diarrhea, leukopenia, and abnormal liver function. All side effects were considered tolerable, and no therapy-related deaths were reported (Table 5).

Table 5:- Side effect after Teysuno treatment

Side effects	case (24)	0	I	II	III	IV
Anorexia	20	10	7	3	0	0
Nausea	17	8	6	2	1	0
Skin pigmentation	19	6	7	4	2	0
Leukopenia	10	5	3	1	1	0
Liver dysfunction	3	2	1	0	0	0
Diarrhea	5	3	1	1	0	0
Stomatitis	5	3	1	1	0	0
Anemia	10	7	2	1	0	0

Figure Legend:-

Figure 1:- Disease free survival (DFS) in Teysuno treated patients. (A) Disease free survival in all 24 treated patients; (B) Disease free survival in patients with less or more 6 months EGFR-TKI treatment.

Figure 1**Discussion:-**

The influence of the individual patient's genetic background on the efficacy of therapy has led to more interest in personalized therapy (13). Personalized therapy is highly attractive in cancer therapy due to a high degree of tumor heterogeneity, resulting in differential responses to treatments (14, 15). Among the established personalized therapies, epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) therapy is one of the most promising strategies (16). Currently, EGFR TKI is the standard treatment in advanced EGFR-mutant Non Small Cell Lung Cancer (NSCLC) patients, with an improvement in response rate, progression free survival, and quality of life compared with standard chemotherapy (17). However, a major weakness of EGFR-TKI therapy is acquired resistance to the EGFR-TKI (7). Furthermore, cancer cells also frequently showed cross-resistance to different drugs. Therefore, few therapeutic strategies are available for the patients that acquire EGFR-TKI resistance, underscoring the need to identify other therapies that could benefit these patients. Here, we demonstrate that Teysuno™ (S-1) therapy is a very promising strategy to control EGFR-TKI resistant NSCLC. We observed an objective response rate (ORR) of 8.3% (2/24) and the disease control rate (DCR) of 50.0% (12/24).

Teysono™ (S-1) is approved for the treatment of advanced gastric cancer and is also being developed for the treatment of hepatocellular carcinoma (11), and other cancers such as breast cancer (18). But, to our knowledge, its efficacy for treating in EGFR-TKI resistant NSCLC patients has not been assessed. One report has investigated the effect of cisplatin plus S-1 in locally advanced NSCLC patients in comparison to, cisplatin plus Tegafur-Uracil (UFT), or 1,1'-cyclobutanedicarboxylate (Carboplatin, CBDCA) plus paclitaxel, and concurrent radiation therapy. In this study, only cisplatin plus S-1 with concurrent radiation therapy significantly reduced tumor stage of the patients

(6). This result suggests that S-1 may not only be effective for EGFR-TKI resistant NSCLC patients, but also for locally advanced NSCLC patients.

The anti-tumor effects of Teysuno is derived from Tegafur, a pro-drug of 5-fluorouracil (5-FU), a DNA damage agent (19). Thus, the anti-tumor effect of Teysuno is not specific, potentially leading to serious side effect, particularly for cancer patients. However, we did not observe significant side effects in our study. Generally, the majority of patients reported improved quality of life. NSCLC symptoms including hemoptysis, cough, dyspnea, and chest pain were significantly reduced after treatment. Furthermore, the body weight, Karnofsky score and KPS score of patients were all are increased significantly after Teysuno therapy. These results indicate that Teysuno is not only an effective treatment for NSCLC, it is also well tolerated and improves patient quality of life.

Our study was relatively small, consisting of 24 EGFR-TKI refractory NSCLC patients. To validate our findings, Teysuno therapy should be tested in different treatment centers using more diverse patient populations. However, our study provides compelling evidence that Teysuno is a suitable therapy for EGFR-TKI refractory NSCLC patients.

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