

A retrospective study of concurrent radiotherapy plus S-1 for treating advanced non-small cell lung cancer

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Abstract

We investigated the efficacy of concurrent radiotherapy plus S-1 (CRS) for treating unresectable stage III advanced non-small-cell lung cancer (ANSCLC).

Seventy five ANSCLC patients were included in this retrospective study. Of those, 40 patients were assigned to an intervention group, and received S-1 (orally at 40 mg/m²) twice daily for 14 consecutive days. Then, concurrent radiotherapy was administered in 2 Gy fractions, 5 times weekly for a total dose of 60 Gy. The other 35 patients were assigned to a control group, and underwent concurrent radiotherapy (the same as the intervention group) and cisplatin (60 mg/m² on day 1 (CRC). The outcome measurements included overall response rate (ORR), overall survival (OS), progression-free survival (PFS), and toxicity.

The 3-year ORR was 60.7% and 43.9% for intervention group and control group, respectively ($P = .031$). The median OS was 34.1 months and 25.3 months in the intervention and control groups, respectively ($P = .041$). The median PFS was 31.5 months for intervention group, while it was 22.4 months for control group ($P = .048$). No significant difference in toxicity was found between the 2 groups.

The results demonstrated that the efficacy of CRS was superior to the CRC in ANSCLC patients with similar toxicity.

Abbreviations: ANSCLC = advanced non-small-cell lung cancer, CRC = concurrent radiotherapy and cisplatin, CRS = concurrent radiotherapy plus S-1, NSCLC = non-small-cell lung cancer, ORR = overall response rate, OS = overall survival, PFS = progression-free survival.

Keywords: cisplatin, concurrent radiotherapy, non-small-cell lung cancer, S-1

1. Introduction

Lung cancer is one of the most common cancers around the world,^[1] especially for non-small-cell lung cancer (NSCLC), which contributes more than 80% of lung cancer.^[2] Of such population, about 30% of them are diagnosed as the stage III disease.^[3] Several randomized controlled trials found that

concurrent chemoradiotherapy is better than chemotherapy for improving the response and survival in those patients.^[4-6] However, more severe toxicity was usually accompanied with such treatment, and 5% of mortality rate related treatment was also found.^[4-6] In addition, most patients with NSCLC experience recurrence. It has been reported that they had about 20% of 5-year survival rate.^[4-6] To further improve the treatment outcome of NSCLC, new agents with fewer adverse effects are needed.

S-1 is one of the most powerful anticancer drugs, and it has been reported to treat NSCLC effectively.^[7] When compared to the other single drugs for metastatic NSCLC, S-1 has been reported as one of the most active response agent.^[8] Previous study have reported that it has 7.1% to 26.7% of response rate, and 7.3 to 16.4 months of median survival time in patients with advanced NSCLC (ANSCLC) who had received treatments previously.^[9-13]

Presently, no study has assessed the concurrent radiotherapy and S-1 (CRS) for the treatment of Chinese patients with stage III ANSCLC. Therefore, this retrospective study explored the efficacy and safety of CRS for treating ANSCLC patients among Chinese population.

2. Patients and methods

This study was formally approved by the ethics committee of The People's Hospital of Fuyang, and Hangzhou Fuyang Hospital of Traditional Chinese Medicine. All patients provided the written informed consent.

In this retrospective study, we included all eligible patients with confirmed diagnosis of unresectable stage IIIA or IIIB

Editor: Fu-Tsai Chung.

This study was funded by Youth Fund of National Natural Science Foundation of China (81403234); Heilongjiang Province Natural Science Fund (H201481); Heilongjiang Province Undergraduate College Young Innovative Talent Training Plan; Doctor Innovation Fund of Heilongjiang University of Chinese Medicine Research Fund (2012bs06).

Competing interests: The authors declare that they have no competing interests.

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Medicine (2018) 97:22(e10740)

Received: 19 December 2017 / Accepted: 24 April 2018

<http://dx.doi.org/10.1097/MD.0000000000010740>

Table 1

Baseline characteristics of patients.

| Variable | | Intervention group (n=40) | Control group (n=35) | P value |
|---------------------------|-----------------|---------------------------|----------------------|---------|
| Age, yrs: mean (SD) | | 62.1 (17.9) | 61.7 (18.3) | .91 |
| Race | Asian (Chinese) | 40 (100.0%) | 35 (100.0%) | 1.00 |
| Gender | Male | 25 (62.5%) | 23 (65.7%) | .77 |
| | Female | 15 (37.5%) | 12 (34.3%) | .77 |
| Performance status (ECOG) | 0 | 26 (65.0%) | 22 (62.9%) | .85 |
| | 1 | 14 (35.0%) | 13 (37.1%) | .85 |
| Histology | Adenocarcinoma | 21 (52.5%) | 18 (51.5%) | .93 |
| | Squamous cell | 15 (37.5%) | 14 (40.0%) | .82 |
| | Large cell | 4 (10.0%) | 3 (8.5%) | 10.83 |
| Phase of disease | IIIA | 30 (75.0%) | 26 (74.3%) | .94 |
| | IIIB | 10 (25.0%) | 9 (25.7%) | .94 |

ECOG=Eastern Cooperative Oncology Group, SD=standard deviation, yrs=years.

ANSCLC^[14] from January 2010 to December 2013. However, we also excluded patients if they had one of the following conditions: pregnant; major organs diseases, and psychiatric disorders that affected the outcome assessments.

All eligible patients with ANSCLC were divided into 2 groups according to the treatments they received. The 40 patients in the intervention group received CRS, while the other 35 patients in the control group underwent concurrent radiotherapy and cisplatin (CRC).

Patients in both groups underwent concurrent radiotherapy with a dose of 2Gy, 5 days weekly for a total of 6 weeks. They all received approximately 40 Gy volumes of concurrent radiotherapy at first, then follow by 20 Gy volumes boost. Additionally, patients in the intervention group received S-1 (orally at 40 mg/m²), twice daily after meals between day 1 and 14, according to a body surface area of different patients. Patients in the control group underwent Cisplatin (60 mg/m²) with a ≥120-minute infusion on the first day and an interval of 4 weeks. It was repeated every 4 weeks for a total of four cycles.

The outcome measurements included the overall response rate (ORR), according to the RECIST criteria,^[15] progression-free survival (PFS), overall survival (OS), and toxicity. Computed tomographic scan, blood and physical examination, and toxicity evaluation were conducted every week throughout the treatment period. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0.^[16]

In this study, the Kaplan–Meier method was used to calculate the OS and PFS. *P*<.05 was considered as a statistical significance.

3. Results

The baseline characteristics are listed in Table 1. There were not significant differences regarding the age, Eastern Cooperative Oncology Group, histological tests, and disease phases between 2 groups.

The ORR was 60.7% in the intervention group, which is significant higher than that of 43.9% in the control group (*P*=.031). The median OS was 34.1 months with range of 6 to 44 months, which was also significantly longer than the control group with median OS of 25.3 months, and ranging 3 to

40 months (*P*=.041; Fig. 1). Furthermore, the median PFS of 31.5 months with range of 5 to 39 months in the intervention group was also much better than that of 22.4 months with range of 3 to 38 months in the control group (*P*=.048; Fig. 2).

The toxicity is showed in Table 2. No significant differences of all toxicities were found between 2 groups. No treatment-related deaths occurred in both groups. The major hematological toxicity included leucopenia (intervention group, 22.5%, vs control group, 20.0%), thrombocytopenia (intervention group, 15.0%, vs control group, 14.3%), neutropenia (intervention group, 15.0%, vs control group, 17.1%), and anemia (intervention group, 12.5%, vs control group 11.4%). The most common grade 3 or 4 nonhematological toxicities were anorexia (intervention group, 12.5%, vs control group, 14.3%).

4. Discussion

S-1 is a novel oral fluorouracil formulation of antitumor drug.^[17] It consists of tegafur (FT), 5-chloro-2, 4-dihydropyridine (CDHP), and potassium oxonate (Oxo) in a ratio of 1:0.4:1.^[18,19] Of these three pharmacological agents, FT is a tumor-selective

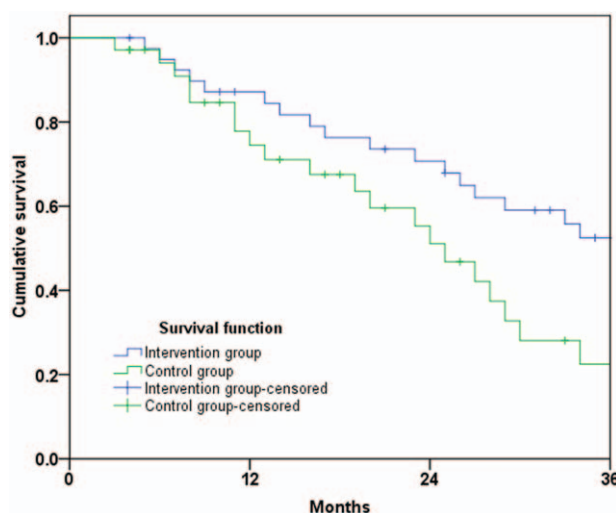


Figure 1. Overall survival.

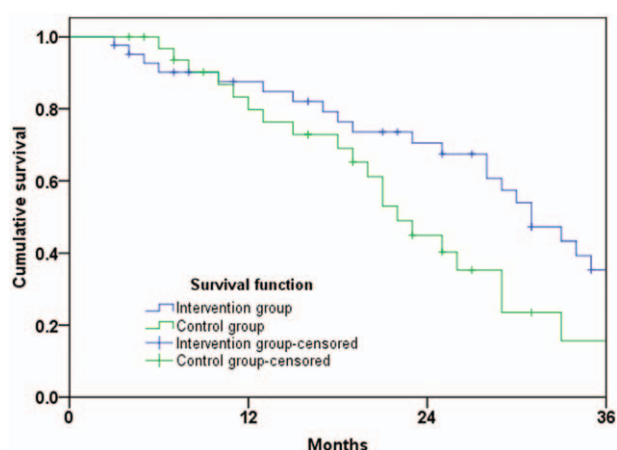


Figure 2. Progression-free survival.

prodrug of 5-fluorouracil (5-FU). CDHP is used to inhibit dihydropyrimidine dehydrogenase (DPD) activity. Oxo is applied to decrease gastrointestinal toxicity.^[18,19] It has been reported that the combination of FT and CDHP is a 180-fold more effective potent for inhibiting DPD in vitro.^[19,20] Additionally, high blood level of 5-Fu concentrations is also reported to sustain in both plasma and in tumors.^[19,20] The other study has reported that S-1 was rapidly absorbed from the gastrointestinal tract. The plasma concentrations of FT and 5-Fu peaked at 1.5 and 3 hours post-treatment, respectively.^[21] On the other hand, the potential reduction gastrointestinal toxicity of Oxo works by inhibiting orotate phosphoribosyl transferase and subsequent 5-Fu phosphorylation or activation in those gastrointestinal tissues.^[21]

Previous studies have shown that S-1 monotherapy appeared to be effective and highly tolerable in patients with advanced/recurrent ANSCLC previously treated with platinum based therapy.^[8,12] Incidences of severe hematological and nonhematological toxicities were relatively low. A phase II study utilized S-1 monotherapy to treat the previously untreated ANSCLC patients. The results found a 22% response rate, 10.2 months median survival time, and also acceptable tolerability.^[8] The other phase II trial of S-1 monotherapy showed an overall response rate of 12.5% and a median survival time of 8.2

Table 2
Summary of toxicity.

| Toxicity | Intervention group (n=40) G3/4 (≥G3) (%) | Control group (n=35) G3/4 (≥G3) (%) | P value |
|-----------------------|--|---|---------|
| Hematologic | | | |
| Leukopenia | 7/2 (22.5%) | 7/0 (20.0%) | .79 |
| Thrombocytopenia | 6/0 (15.0%) | 5/0 (14.3%) | .93 |
| Neutropenia | 5/1 (15.0%) | 6/0 (17.1%) | .80 |
| Anaemia | 5/0 (12.5%) | 4/0 (11.4%) | .89 |
| Nonhematologic | | | |
| Anorexia | 4/1 (12.5%) | 5/0 (14.3%) | .82 |
| Nausea | 2/1 (7.5%) | 3/0 (8.6%) | .86 |
| Fatigue | 3/0 (7.5%) | 2/0 (5.7%) | .76 |
| ALT, AST | 2/0 (5.0%) | 2/0 (5.7%) | .89 |
| Pneumonitis | 2/0 (5.0%) | 0/0 (0%) | .33 |
| Diarrhea | 1/0 (2.5%) | 2/0 (5.7%) | .49 |

ALT=alanine aminotransferase, AST=aspartate aminotransferase.

months,^[12] with Grade 3 hematological toxicities of neutropenia and anemia in one patient respectively.

Previous studies have proven that the combination chemotherapy of S-1 and other agents have encouraging effect to treatment ANSCLC.^[22-25] However, the optimal sequence for the administration of these drugs has yet to be determined. This study investigated the combination use of the CRS for treating stage III ANSCLC among Chinese population. The results of this study indicated reasonable survival with a median OS of 34.1 months and a three-year ORR of 60.7%. Additionally, the data of toxicities have showed that CRS had a favorable toxicity profile. The overall frequency of toxicity was similar in 2 groups.

This study has 2 limitations. First, the sample size is relative small, which may affect our results. Then, the treatment period is pretty short. Thus, the efficacy and safety of longer period of treatment of such schedule still needs to be explored.

5. Conclusion

The results of this retrospective study demonstrated the promising efficacy and an acceptable toxicity profile of CRS for treating patients with ANSCLC. Further studies are still needed to warrant the results of this study.

Author contributions

DZ conceived of the study, participated in the coordination and design of the study, performed. JF performed the statistical analysis and wrote the paper. XW and DZ carried out the clinical assessment and participated in most parts of the study. All authors read and approved the final manuscript.

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