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ORIGINAL ARTICLE

Curative effect of hyperfractionated accelerated radiotherapy combined with EP chemotherapy regimen on limited-stage small cell lung cancer

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Summary

Purpose: *The purpose of this study was to explore the curative effect and safety of hyperfractionated accelerated radiotherapy (HART) and conventional fractionated radiotherapy (CFRT) combined with EP chemotherapy regimen in the treatment of limited-stage small cell lung cancer (LS-SCLC).*

Methods: *A total of 148 patients with LS-SCLC were retrospectively analyzed. 74 cases underwent HART combined with EP chemotherapy regimen (HART group), while the remaining 74 cases underwent CFRT combined with EP chemotherapy regimen (Control group). The short-term response rate and quality-of-life score were compared between the two groups. Then the patients were followed up, and the survival status of them was recorded.*

Results: *The curative effect was evaluated in all patients at 2 months after treatment. The overall response rate was 86.5% and 68.9%, respectively, in HART group and Control group. After treatment, the scores of physical function, role function, cognitive function, emotional function, social function and general health status were all higher in HART group than those in Control group. In HART group, the score of nausea/vomiting was significantly higher than that in Control group. The median overall survival (OS) was 23.6 months and 20.2 months, and the 3-year OS rate was 21.6% and 14.9%, respectively, in HART group and Control group. The results of log-rank test revealed that the OS rate had a statistically significant difference between the two groups, and it was remarkably superior in HART group to that in Control group.*

Conclusions: *HART combined with EP chemotherapy regimen has a better curative effect on LS-SCLC than conventional radiotherapy, and the survival rate of patients is higher, without significantly increasing adverse reactions and significantly reducing quality of life, so it is worthy of clinical popularization.*

Key words: *hyperfractionated accelerated radiotherapy, chemotherapy, EP regimen, small cell lung cancer, limited stage, curative effect*

Introduction

Small cell lung cancer (SCLC) patients account for approximately 10-20% of lung cancer patients, about 40% of whom are in the limited stage. Limited-stage SCLC (LS-SCLC) is characterized by proneness to recurrence and metastasis, rapid proliferation and poor prognosis, greatly threatening the life safety of patients [1,2]. At present, thoracic radiotherapy combined with EP chemotherapy regimen is the standard clinical treatment method for LS-SCLC. LS-SCLC is sensitive to chemoradiotherapy, so chemoradiotherapy can reduce the local recurrence rate and increase the 2-year survival rate by 5-7% compared with chemotherapy [3,4]. However, there are still great controversies about

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the target area range, radiotherapy technique, total radiation dose, and time fractionation method in the treatment of LS-SCLC.

SCLC has been mostly in the late stage when diagnosed, so fractionated radiotherapy is dominated in the radiotherapy regimen. With the development of medical technology, the idea of hyperfractionated accelerated radiotherapy (HART) has been proposed, and it is believed that this method should be theoretically superior to conventional fractionated radiotherapy (CFRT) [5-7]. However, some experts have also argued that HART may increase the toxic adverse effects of treatment, which lacks unified conclusion. In this study, the curative effect and safety were compared between HART and CFRT combined with EP chemotherapy regimen in the treatment of LS-SCLC, so as to provide a strong basis for selecting the therapeutic regimen for such patients.

Methods

General data

The clinical data of 148 patients with LS-SCLC were collected. Inclusion criteria: 1) patients diagnosed by cytology or pathology, 2) newly-diagnosed patients, 3) those diagnosed with LS-SCLC through chest CT, bone CT and brain CT, 4) those with at least one measurable lesion, 5) those with a Karnofsky performance scale score ≥70 points, 6) those without major organ dysfunction, and with basically normal blood routine, hepatic-renal function and heart function, and 7) those with an expected survival time >3 months. Exclusion criteria: 1) patients in extensive stage, 2) those who could not tolerate chemoradiotherapy due to dysfunction in the heart, liver or kidney, 3) those with a history of myocardial infarction in the past 6 months, or 4) those who used to undergo surgery or other treatments. 74 cases underwent HART combined with EP chemotherapy regimen (HART group), while the remaining 74 cases underwent CFRT combined with EP chemotherapy regimen (Control group). There were 99 males and 49 females aged 41-77 years old, with a median of 54.34 years old. The baseline characteristics of patients in the two groups before treatment are shown in Table 1, and they had no statistically significant differences (p>0.05). This study was approved by the Ethics Committee of The First Affiliated Hospital of Nanhua University, and all patients enrolled were informed of the study according to the *Declaration of Helsinki* and signed the informed consent.

Therapeutic regimen

All patients were treated with intensity modulated radiotherapy combined with standard EP chemotherapy regimen. Standard EP chemotherapy regimen: intravenous infusion of etoposide (Sichuan Sunny-

Table 1. Baseline demographic and clinical characteristics of the studied patients

Indicators	*HART group (n=74)* *n (%)*	*Control group (n=74)* *n (%)*	*p*
Age (years old)	53.86±9.51	55.01±9.66	0.467
Gender (Male/ Female)	47/27	52/22	0.485
Smoking history			0.369
Yes	49 (66.2)	55 (74.3)	
No	25 (33.8)	19 (25.7)	
Tumor type			0.509
Central type	38 (51.4)	43 (58.1)	
Peripheral type	36 (48.6)	31 (41.9)	
Largest tumor diameter (cm)	3.36±1.07	3.29±1.11	0.597
T stage			0.687
T1	9 (12.2)	7 (9.5)	
T2	19 (25.7)	21 (28.4)	
T3	22 (29.7)	18 (24.3)	
T4	24 (32.4)	28 (37.8)	
N stage			0.547
N0	8 (10.8)	11 (14.9)	
N1	12 (16.2)	14 (18.9)	
N2	54 (72.9)	49 (66.2)	
KPS score			0.408
80-90	44 (59.5)	39 (52.7)	
70-80	30 (40.5)	35 (47.3)	

HART: Hyperfractionated accelerated radiotherapy; KPS: Karnofsky performance status.

Hope Pharmaceutical Co., Ltd., Chengdu, China, NMPN H20045483) on d 1-5 (75 mg/m^2) combined with cisplatin [Qilu Pharmaceutical (Hainan) Co., Ltd., Haikou, China, NMPN H20073652] on d 1-3 (30 mg/m^2). Chemotherapy was performed for 4 cycles (21 d/cycle) in both groups, during which symptomatic treatment such as vomit-stopping and liver-protecting therapy could be given. EP chemotherapy was also needed for 2 cycles simultaneously during radiotherapy.

All patients underwent three-dimensional conformal radiotherapy. The CT scanner was used for tumor positioning in patients in a supine and fixed position, and then the CT simulation system was used for radiotherapy planning. The gross tumor volume included the primary lesion and metastatic lymph nodes, the target area was delineated, and the radiotherapy plan was optimized using the dose-volume histogram. Patients in Control group were treated with CFRT: Radiotherapy was conducted once a day (5 d/week) at a total dose of 56 Gy and a fractional dose of 2 Gy. In HART group, HART was conducted twice a day (5 d/week) at an interval of 8 h at a total dose of 50 Gy and a fractional dose of 1.5 Gy.

Observation indexes

Short-term curative effect: The short-term curative effect was assessed at 2 months after treatment. According to the Response Evaluation Criteria in Solid Tumors 1.0 (RECIST 1.0), the short-term curative effect is classified into complete response (CR, the tumor completely disappears), partial response (PR, the sum of the maximum diameter of baseline lesions declines by at least 30%), stable disease [SD, the sum of the maximum diameter of baseline lesions declines but less than PR, or rises but less than progressive disease (PD)] and PD (the sum of the maximum diameter of baseline lesions rises by at least 20% or there are new lesions). Total response rate = (CR + PR)/total cases×100%.

Adverse reactions: During chemotherapy, blood routine test was performed twice a week, and hepatic-renal function and electrocardiogram examinations were performed before each cycle of chemotherapy. Before each cycle of chemotherapy or radiotherapy, the patients underwent chest CT and color Doppler ultrasonography of the adrenal glands, liver and retroperitoneal lymph nodes, and also received the hepatic-renal function and blood biochemical examinations to determine the curative effect and toxicity of the treatment method on the patients. Radiation esophagitis and radiation pneumonitis were assessed based on the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) standards, and the toxicity of chemotherapy was evaluated according to the Common Terminology Criteria for Adverse Events v3.0. The EORTC Quality of Life Questionnaire-Core 30 (QLQ-30) was used to score the quality of life after treatment.

Follow-up of survival status: The patients were followed up every 3 months within 2 years and every 6 months after 2 years, and the overall survival (OS, the duration from enrollment to death for any reason) and progression-free survival (PFS) of all patients were recorded. Those lost to follow-up were considered as censored data from the date of loss.

Statistical analysis

Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Measurement data were expressed as mean ± standard deviation (x±s), and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. The survival analysis was performed using the Kaplan-Meier method, and log-rank test was adopted. $p<0.05$ suggested the statistically significant difference.

Results

Comparison of short-term curative effect

The curative effect was evaluated in all patients at 2 months after treatment. In HART group, there were 27 CR cases (36.5%), 37 PR cases (50.0%), 8 SD cases (10.8%) and 2 PD cases (2.7%), with a overall response rate of 86.5% (64/74). In Control group, there were 20 CR cases (27.0%), 31 PR cases (41.9%), 18 SD cases (24.3%) and 5 PD cases (6.8%), with a overall response rate of 68.9% (51/74). It could be observed that the overall response rate had a statistically significant difference between the two groups, which was significantly better in HART group than that in Control group (p=0.011) (Table 2).

Table 2. Comparison of tumor response between the two groups of patients

Indicators	*HART group (n=74)* *n (%)*	*Control group (n=74)* *n (%)*	*p*
CR	27 (36.5)	20 (27.0)	
PR	37 (50.0)	31 (41.9)	
SD	8 (10.8)	18 (24.3)	
PD	2 (2.7)	5 (6.8)	
ORR (CR + PR)	64 (86.5)	51 (68.9)	0.011

HART: Hyperfractionated accelerated radiotherapy; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Overall response rate.

Comparison of EORTC QLQ-30 score after treatment

EORTC QLQ-30 contains a total of 30 items, including 5 functional domains (physical function, role function, cognitive function, emotional function, and social function), 3 symptom domains (fatigue, pain, and nausea/vomiting), general health status and 6 single items. After treatment, the scores of physical function, role function, cognitive function, emotional function, social function and general health status were all higher in HART group than those in Control group, but the differences were not statistically significant (p>0.05). In HART group, the scores of fatigue and pain were lower than those in Control group, showing no statistically significant differences (p>0.05), but the score of nausea/vomiting was greatly higher than that in Control group (p=0.047). In terms of single items, there were no statistically significant differences in the scores of dyspnea, loss of appetite, diarrhea, constipation, insomnia and financial difficulty between the two groups (p>0.05) (Table 3).

Comparison of adverse reactions

The treatment-related adverse reactions mainly included leukopenia, anemia, thrombocytopenia, gastrointestinal reactions, radiation pneumonitis, radiation esophagitis, radiation pericarditis and liver damage (Table 4). The incidence of adverse reactions after treatment had no statistically significant differences between the two groups (p>0.05). In the two groups, leukopenia occurred in 12 cases (16.2%) and 16 cases (21.6%) (p=0.401), anemia in

Table 3. Comparison of posttreatment EORTC QLQ-30 scores between the two groups of patients

Indicators	*HART group (n=74)*	*Control group (n=74)*	*p*
Functional scale			
Physical	78.69±13.48	76.20±13.80	0.275
Role	58.33±14.69	57.17±14.59	0.509
Emotional	75.74±15.54	74.14±14.96	0.578
Cognitive	74.14±13.50	73.03±14.14	0.626
Social	62.93±15.11	62.03±15.02	0.573
General health condition	64.08±15.75	62.23±16.36	0.485
Symptom scale			
Fatigue	39.03±4.57	39.54±4.78	0.556
Pain	33.29±4.69	33.88±4.90	0.580
Nausea / vomiting	9.70±4.58	8.84±4.50	0.047
Single items			
Dyspnea	34.23±5.13	34.89±5.72	0.493
Appetite loss	15.63±5.89	14.91±5.22	0.581
Diarrhea	9.16±4.94	9.02±4.83	0.625
Constipation	18.17±6.47	17.79±6.12	0.587
Insomnia	21.31±6.77	20.90±5.80	0.490
Financial difficulty	63.38±7.14	63.92±7.87	0.442

HART: Hyperfractionated accelerated radiotherapy.

Table 4. Comparison of adverse reactions between the two groups of patients

Indicators	*HART group (n=74)* *n (%)*	*Control group (n=74)* *n (%)*	*p*
Leukopenia	12 (16.2)	16 (21.6)	0.401
Anemia	23 (31.1)	26 (35.1)	0.503
Thrombocytopenia	21 (28.4)	13 (17.6)	0.118
Gastrointestinal reactions	52 (70.3)	42 (56.8)	0.088
Radiation pneumonitis	8 (10.8)	5 (6.8)	0.364
Radiation esophagitis	8 (10.8)	6 (8.1)	0.574
Radiation pericarditis	11 (14.9)	7 (9.5)	0.314
Liver function damage	19 (25.7)	24 (32.4)	0.365

HART: Hyperfractionated accelerated radiotherapy.

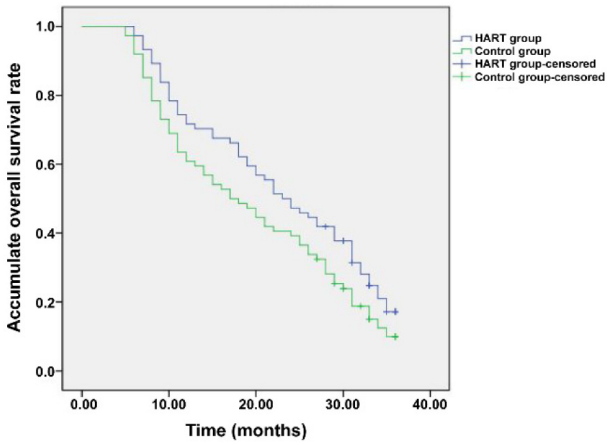

Figure 1. Kaplan-Meier survival curves of patients in HART group and Control group. The overall survival rate of patients in HART group was significantly higher than that in Control group (p=0.032).

23 cases (31.1%) and 26 cases (35.1%) (p=0.503), thrombocytopenia in 21 cases (28.4%) and 13 cases (17.6%) (p=0.118), gastrointestinal reactions in 52 cases (70.3%) and 42 cases (56.8%) (p=0.088), radiation pneumonitis in 8 cases (10.8%) and 5 cases (6.8%) (p=0.364), radiation esophagitis in 8 cases (10.8%) and 6 cases (8.1%) (p=0.574), radiation pericarditis in 11 cases (14.9%) and 7 cases (9.5%) (p=0.314), and liver damage in 19 cases (25.7%) and 24 cases (32.4%) (p=0.365), displaying no statistically significant differences. Most of the adverse reactions were controllable and mainly in grade I-II, which were all improved after symptomatic treatment.

Follow-up results of survival status

All of the 148 patients were followed up until May 2020, with a median follow-up time of 6-36 months [(29.6±7.8) months]. During the follow-up period, the median OS was 23.6 months and 20.2 months, the 1-year OS rate was 71.6% (53/74) and 60.8% (45/74), the 2-year OS rate was 47.3% (35/74) and 39.2% (29/74), and the 3-year OS rate was 21.6% (16/74) and 14.9% (11/74), respectively, in HART group and Control group. The survival curves of patients were plotted using Kaplan-Meier method (Figure 1). The results of log-rank test revealed that the OS rate had a statistically significant difference between the two groups, and it was remarkably superior in HART group to that in Control group (p=0.032).

Discussion

LS-SCLC is a systemic disease, and mediastinal lymph node metastasis or distant metastasis occurs in most patients at the time of diagnosis. In clinical treatment, the survival time of patients is prolonged and the prognosis is improved mainly through controlling the primary lesions and distant metastasis [8]. LS-SCLC is highly sensitive to chemotherapy due to its special biological behaviors. However, the efficacy of chemotherapy alone is unsatisfactory due to drug resistance, and primary lesions will relapse in more than 80% of patients, with higher recurrence and metastasis rates [9]. Thoracic radiotherapy can reduce local recurrence to different degrees, thereby prolonging the survival time of patients. Radiotherapy combined with chemotherapy has gradually become the standard treatment pattern for LS-SCLC [10].

Three-dimensional conformal radiotherapy technique can raise the radiation dose on tumor tissues while avoiding radiation in the surrounding normal tissues. At present, the condition of lung cancer has been controlled for a long time or the patients have been in a long-term PFS state after three-dimensional conformal radiotherapy [11]. Some research results also showed that three-dimensional conformal radiotherapy has a good curative effect on patients with locally advanced lung cancer, which can not only benefit patients to the greatest extent, but also produce well-tolerable adverse reactions [12]. When three-dimensional conformal radiotherapy technique is used, there is a need to prevent tumor tissues from detaching from the target area and abnormal damage during treatment, and such a requirement can be exactly met by HART used in this study. Currently, it has been confirmed that HART has a good killing effect on tumor cells, but the dose control of this pattern on various tissues remains controversial [13,14]. There is also a study showing that the therapeutic effect of HART is better than that of CFRT, and the survival rate of patients receiving HART is improved, but the incidence rate of adverse reactions also significantly rises [15]. In this study, three-dimensional conformal radiotherapy was mainly used, with a significantly improved accuracy, in which the target area delineated became markedly smaller. In the early stage of treatment, 4 cycles of EP chemotherapy regimen were adopted, and then EP chemotherapy regimen combined with HART was used in the late stage. As a result, the proliferation of tumor cells in the intermittent period of the treatment cycle was obviously controlled, and the occurrence of acquired tolerance was effectively controlled, thereby reducing the accelerated repopulation of cancer cells during treatment.

The total dose of CFRT and HART is 56 Gy and 50 Gy, respectively. It can be seen that the total dose of HART is lower than that of CFRT, but the results revealed that the total response rate of HART

(86.5%) was obviously higher than that of CFRT (68.9%) in this study, consistent with the research results of other scholars [16,17]. Besides, it was found through the 3-year follow-up that the survival rate of patients undergoing HART was also obviously higher than that of patients undergoing CFRT.

The patients selected in this study were all in limited stage. In the case of no tumor cell metastasis and spread, patients can benefit the most from HART. Lung cancer cells are characterized by rapid proliferation, and the number of them will double generally in only 2-3 d. It has been even found through some research results that the survival probability of lung cancer patients undergoing treatment for 1 h every night will be reduced by about 2% [18,19]. On the contrary, HART can shorten the total treatment time, thus lowering the risk of tumor cell proliferation. In theory, the higher the radiation dose, the better the killing effect on tumor cells, so the overall duration is shortened but the dose is increased in the radiotherapy regimen [20]. In this study, although adverse reactions occurred in a considerable number of patients during treatment, the differences were not statistically significant except gastrointestinal reactions ($p>0.05$), indicating that the safety is similar between CFRT and HART. The possible reason is that the radiotherapy dose was increased but the duration was shortened in HART group, which still needs in-depth research. Moreover, the quality-of-life scores, except nausea/vomiting score, had no statistically significant differences between the two groups ($p>0.05$).

This single-center retrospective study has some limitations. For example, the sample size was not large enough, the follow-up period was short, the follow-up content was not comprehensive enough, and the possible influence of different radiotherapy methods on the tumor progression in patients was not explored. In the future, the results in this study remain to be further proved by prospective multi-center, randomized controlled studies with a large sample size, so as to provide references for selecting the therapeutic regimen for LS-SCLC.

Conclusions

HART combined with EP chemotherapy regimen has a better curative effect on LS-SCLC than conventional radiotherapy, and the survival rate of patients is higher, without significantly increasing adverse reactions and significantly reducing quality of life, so it is worthy of clinical popularization.

Conflict of interests

The authors declare no conflict of interests.

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