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Clinical Study of Oxaliplatin Injection and Fluorouracilinjection Plus Irinotecan Injection in the Treatment of Elderly Patients with advanced Liver Cancer

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Abstract: Objective *To discuss the efficacy and safety ofOxaliplatin and Fluorouracilplus irinotecan in second-line treatment of elderly patients with advanced liver cancer.* ***Methods:*** *60 advanced liver cancer patients, who failed, who failed to treat in the first-line treatment using fluorouracil combined with oxaliplatin , were randomly divided into experimental group(n=60) and control group(n=60). The control group was given intravenous infusion (15min) of 3mg/m2 on 2 d, and also given intravenous infusion (120min) of irinotecan 300mg/m2. On 1 d the experimental group was given intravenous infusion (15min) ofOxaliplatin 7.5mg/kg plus saline 100mL on the basis of the control group. The two groups was two cycles with twenty-one days per cycle.The clinical efficacy, progression free survival , overall survival, and the side effects of the drugs were compared between the experimental group and the control group in elderly patients with advanced liver cancer.* ***Results:*** *The disease progressions were 30% and 56.67% in the experimental group and the control group respectively (P<0.05); the objective response rates were 40% and 16.67% in the experimental group and the control group respectively (P<0.05); the disease control rate was 70% and 43.33% in the experimental group and the control group respectively (P<0.05); the median OS was 14 months (95% CI: 8.7~17.9) in the experimental group and the median OS was 11 months (95% CI: 5.1~13.9) in the control group, more importantly,the difference was significant (P<0.05);the median PFS was 5 months (95%CI: 4.3~7.2) in the control group and the median PFS was 8 months (95% CI: 6.5~8.2) in the experimental group, more importantly,the difference was significant (P<0.05); the myelosuppression, nausea, vomiting, fatigue and transaminase abnormalities were more obvious in the experimental group and the control group, especiallyI-II grade toxicity; the incidence of neutropenia in the experimental group was higher than that in the control group (46.67% vs 20.00%, P=0.028); the incidence of nausea and vomiting grade I-II in the experimental group was higher than that in the control group (43.33% vs 16.67%, P=0.024).* ***Conclusion:*** *Oxaliplatin combined with Fluorouraciland irinotecan in patients with advanced liver cancer could not only improve ORR and DCR, but also prolonged PFS and OS, Although this chemotherapy produced a certain adverse drug reaction, it was acceptable.*

Keywords: *Oxaliplatin, Fluorouracil, Irinotecan, liver cancer, Advanced*

Liver cancer is one of the most common digestive cancers in clinic. Its incidence rate and mortality rate are increasing year by year in China. [1-3] Because most patients lack typical clinical manifestations in the early stage and are difficult to be found, they are in the late stage when they see a doctor. At this time, they have lost the opportunity of surgery. Chemotherapy has become the main means of advanced liver cancer in the elderly [4, 5]. 5-fluorouracil based chemotherapy has always been used as its first-line chemotherapy, but for patients who fail, how to choose a more effective second-line chemotherapy is particularly important. In recent years, with the continuous development of new drugs, a large number of chemotherapeutic drugs have been used in clinic. There are more and more reports on the treatment of advanced elderly liver cancer with the combined second-line chemotherapy regimen of letitrexed and irinotecan, but there is no report on the combination ofOxaliplatin with letitrexed and irinotecan. This study has achieved satisfactory clinical results by

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using the above triple scheme, which is reported as follows.

1. Materials, Objects and Methods

1.1 Study Design

This protocol is designed according to the prospective, randomized, single blind, controlled and single center clinical research method.

1.2 Case Selection

120 elderly patients with advanced liver cancer who the first-line fluorouracil combined with oxaliplatin from January 2014 to December 2020 were selected. This study was approved by the ethics committee of our hospital. All patients included in the study signed informed consent.The diagnosis and inclusion criteria refer to the relevant diagnostic criteria in the code for diagnosis and treatment of liver cancer (2010 Edition). 1) Age ≥ 18, regardless of gender; 2) The survival time of patients was predicted to be more than 3 months; 3) The blood routine and liver and kidney functions of all subjects were normal before chemotherapy; 4) Quality of life score ≥ 60; 5) Patients with failure of first-line fluorouracil combined with oxaliplatin; 6) The ECoG physical status score ranges from 0 to 2.Exclusion criteria 1) patients with severe infection or mental illness; 2) Patients with other malignant tumors or allergic to chemotherapeutic drugs; 3) Patients with liver, kidney, heart and other serious organ lesions who can not tolerate chemotherapy; 4) Patients with abnormal coagulation function and gastrointestinal bleeding.

1.3 Drugs and Instruments

Oxaliplatin injection, specification: 100mg / 4ml each, batch No.: 20120068, produced by Roche pharmaceutical company, Switzerland; Letitrexed injection, specification: 2mg each, batch No.: 20080902, produced by Nanjing Zhengda Tianqing Pharmaceutical Co., Ltd; Irinotecan injection, specification: 100mg each, batch No.: 20040701, produced by Jiangsu Hengrui Pharmaceutical Co., Ltd.Discovery LS PET / CT all-in-one machine is a product of general electric medical devices (GE).

1.4 Grouping and Treatment

120 patients were randomly divided into control group and experimental group. The control group: the next day, intravenous drip of letitrexed 3mg / m2 for 15min; On the second day, irinotecan 300 mg / m2 was injected intravenously for 120 min. Treatment plan of the experimental group: on the basis of the control group,Oxaliplatin 7.5mg/kg + 100ml normal saline was intravenously injected for 90min on the first day (the patients with the first infusion were well tolerated, and the time of the second infusion could be adjusted to 60min). The patients in both groups were treated for two cycles after 21 days.

1.5 Observation Index and Curative Effect Evaluation

All patients included in the study were followed up at least once by telephone or outpatient. The start time of follow-up is after the end of chemotherapy (i.e. after two cycles), and the end time of follow-up is when the patient dies or ends in May 2017. The progression free survival (PFS) and overall survival (OS) of all patients were counted. PFS: the time from the beginning of chemotherapy to disease progression or patient death. OS: time from the beginning of chemotherapy to the end of death or follow-up.

The short-term efficacy of elderly patients with advanced liver cancer was evaluated according to the evaluation criteria of chemotherapy efficacy of solid tumors formulated by who, including complete remission (CR), partial remission (PR), disease stability (SD) and disease progression (PD). Cr: the tumor disappeared completely after treatment. And can last for more than 4 weeks; PR: after treatment, the product of the maximum vertical diameter and the maximum diameter of the tumor decreased by 50%; And last for at least 4 weeks; SD: the product of the maximum vertical diameter and the maximum diameter of the tumor decreased but did not reach PR and increased but did not reach PD; PD: after treatment, the product of the maximum vertical diameter and the maximum diameter of the tumor increased by more than 25%. Objective response rate (ORR) = Cr + PR, disease control rate (DCR) = Cr + PR + SD. Evaluation was performed after two cycles of treatment.

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After one cycle of treatment, the adverse reactions were evaluated and graded according to NCI-CTC (version 4.0). During the study period, if the patient is unable to tolerate chemotherapeutic drugs or the disease progresses, the investigator will choose to terminate the study if necessary.

1.6 Statistical Treatment

Spss21.0 was used for statistical analysis. Measurement data are expressed as $\bar{x} \pm s$,Conduct t-test; Count data is expressed as rate (%), rows χ 2 inspection; Kaplan Meier method was used to describe the survival curve, and log rank test was used to compare the differences of survival curve. $P < 0.05$, the difference was statistically significant.

2. Result

2.1 General Information

There was no significant difference in general data between the two groups ($P > 0.05$), as shown in Table 1.

Table 1: Comparison of general information in two groups($\bar{x} \pm s$)

Item	Control(n=60)	Treatment(n=60)
Age (year)	47.35±4.12	48.17±3.59
Sex(M/F)	46/14	50/10
ECOG(n, %)		
0	14 (23.33)	12 (20.00)
1	30 (50.00)	26 (43.33)
2	16 (26.67)	22 (36.67)
Tumour type(n, %)		
Transverse colon cancer	22 (36.67)	20 (33.33)
Carcinoma of descending colon	10 (16.67)	12 (20.00)
Carcinoma of sigmoid	8 (13.33)	12 (20.00)
Rectum cancer	20 (33.33)	16 (26.67)

ECOG: Eastern cooperative oncology group; Control group:300mg.m^{-2} irinotecan+ 3 mg.m^{-2} pemetrexed; Treatment group:7.5mg.kg^{-1}Oxaliplatin+3mg.m^{-2} pemetrexed+300mg.m^{-2} irinotecan

2.2 Comparison of Clinical Efficacy between the Two Groups

After treatment, the PD of the experimental group was 30.00% (18 / 60 cases) and that of the control group was 56.67% (34 / 60 cases), the difference was statistically significant ($P < 0.05$); The orr of the experimental group was 40.00% (24 / 60 cases) and that of the control group was 16.67% (10 / 60 cases), the difference was statistically significant ($P < 0.05$); The DCR of the experimental group was 70.00% (42 / 60 cases) and that of the control group was 43.33% (26 / 60 cases). The difference was statistically significant ($P < 0.05$). See Table 2.

Table 2: Comparison of clinical effect in two groups (n, %)

Efficacy (n, %)	Control(n=60)	Treatment(n=60)
CR	2 (3.33)	10 (16.67)
PR	8 (13.33)	14 (23.33)
SD	16 (26.67)	18 (30.00)
PD	34 (56.67)	18 (30.00) *
ORR	10 (16.67)	24 (40.00) *
DCR	26 (43.33)	42 (70.00) *

CR: Complete remission; PR: Partial response; SD: Stable disease; PD: Progressive disease; Compared with control group, * $P<0.05$

2.3 Comparison of PFS and OS between the two Groups

After treatment, the median OS in the experimental group was 14 months (95% CI: 8.7 ~ 17.9),

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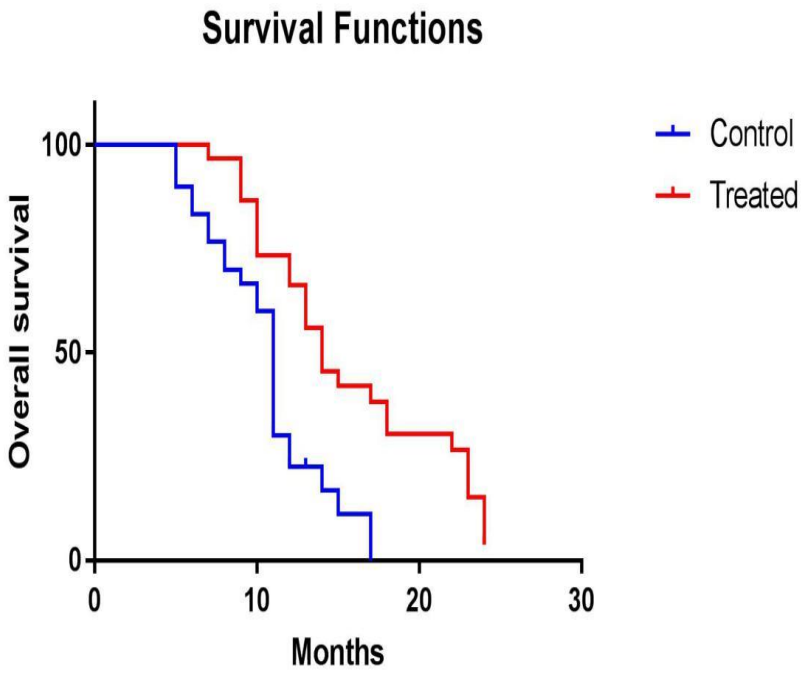
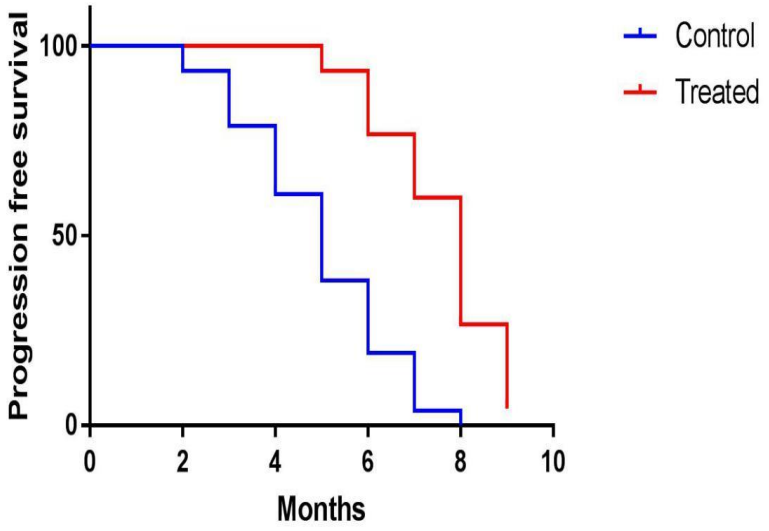
and that in the control group was 11 months (95% CI: 5.1 ~ 13.9); The median PFS of the experimental group was 8 months (95% CI: 6.5 ~ 8.2), and that of the control group was 5 months (95% CI: 4.3 ~ 7.2). The difference was statistically significant (P < 0.05). See Figure 1-2.



Picture 1: Comparison of overall survival in two groups



Picture 2: Comparison of progression free survival in two groups

2.4 Comparison of Adverse Drug Reactions between the Two Groups

Bone marrow suppression, nausea and vomiting, fatigue and transaminase abnormalities were more obvious in the two groups, mainly grade I - II toxic and side effects. The incidence of grade I - II toxic and side effects of neutropenia in the experimental group was higher than that in the control group (46.67% vs 20.00%, P = 0.028); The incidence of grade I-II toxic and side effects of nausea and vomiting in the experimental group was higher than that in the control group (43.33% vs 16.67%, P = 0.024), as shown in Table 3.

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Table 3: Comparison of toxicity effects in two groups (n, %)

Toxicity effect	I-II		III-IV	
	Control(n=60)	Treatment(n=60)	Control(n=60)	Treatment(n=60)
Hematologic toxicity				
Leukopenia	22 (36.67)	26 (43.33)	6 (10.00)	8 (13.33)
Neutropenia	12 (20.00)	28 (46.67)	34 (56.67)	18 (30.00)
Hemoglobin	24 (40.00)	22 (36.67)	4 (6.67)	2 (3.33)
Thrombocytopenia	14 (23.33)	16 (26.67)	2 (3.33)	2 (3.33)
Non-hematological toxicity				
Diarrhea	2 (3.33)	2 (3.33)	0 (0.00)	0 (0.00)
Nausea and vomiting	10 (16.67)	26 (43.33)	2 (3.33)	2 (3.33)
Sensory neuropathy	4 (6.67)	6 (10.00)	2 (3.33)	2 (3.33)
Fatigue	18 (30.00)	24 (40.00)	2 (3.33)	2 (3.33)
Alopecie	2 (3.33)	0 (0.00)	0 (0.00)	18 (30.00)
Mucositis	0 (0.00)	18 (30.00)	0 (0.00)	0 (0.00)
AST/ALT	18 (30.00)	24 (40.00)	2 (3.33)	2 (3.33)

3. Discuss

Advanced liver cancer, especially elderly advanced liver cancer, is often given 5-fluorouracil-based first-line chemotherapy drugs. It is reported in the literature that the effective rate of the combined chemotherapy scheme is as high as 50% [6]. However, for patients who fail in the first-line treatment, the effect of continuing to use 5-fluorouracil-based second-line chemotherapy drugs is not very satisfactory. Foreign literature reports that after the failure of 5-fluorouracil-based first-line chemotherapy for elderly patients with advanced liver cancer, FOLFOX regimen is used as its second-line chemotherapy regimen, and the effective rate is as low as 30% [7]; Similarly, there are similar literature reports in China. For elderly patients with advanced liver cancer who failed FOLFOX first-line treatment, FOLFIRI second-line chemotherapy is still low. Therefore, it is very important to find an effective chemotherapy scheme for the failure of first-line chemotherapy for elderly advanced liver cancer [8, 9]

Letitrexed is a thymus synthase inhibitor. What it really plays a role is its metabolite polyglutamic acid, which has stronger thymus enzyme inhibition [10 11], and finally leads to cell death. It is reported that it has stronger antitumor activity than 5-fluorouracil and low adverse reactions [12]. Irinotecan is a topoisomerase specific inhibitor. Its mechanism is to cause cell DNA strand breakage, resulting in cell death [13]. The mechanisms of action of the two drugs are completely different. Therefore, it is of great significance to study whether retitrexed combined with irinotecan has stronger antitumor activity in the second-line treatment of elderly patients with advanced liver cancer. Although this combined regimen has been reported abroad, there have been many reports in China. Zhou Jianhong and other [14] pointed out that the effective rate of letitrexed combined with irinotecan is 23.88%, the median PFS and 0s are 3.7 months and 7.8 months respectively, and the incidence of diarrhea in grade III ~ IV toxic and side effects is 1.49%. The effective rate in this study was 43.33%. The median PFS and 0s were 8 months and 14 months respectively, which was similar to the above literature reports, but there was no grade III ~ IV diarrhea. It may be related to the different drug doses of the patients included in the study [15, 16]. Therefore, we can boldly speculate that letitrexed combined with irinotecan may have synergistic effect and play a more antitumor activity.

Bevacizumab is a vascular endothelial growth factor inhibitor, which can inhibit the mitosis of endothelial cells by combining with vascular endothelial growth factor in tumor cells, reduce the formation of neovascularization, and finally effectively inhibit the growth of tumor by reducing the blood supply of tumor cells [17]. Foreign literature reports thatOxaliplatin included in the second-line treatment can significantly improve the PFS, OS and objective remission rate of patients [18]. AlthoughOxaliplatin has achieved satisfactory results in the second-line treatment after the failure of the first-line treatment in elderly patients with advanced liver cancer, and the above-mentioned regimen of retitrexed combined with irinotecan also achieve satisfactory clinical results, the combination of the three drugs as the second-line treatment has not been reported. From this point of view, 30 patients were selected for the combination of retitrexel and irinotecan, and the other 30 patients were selected for the triple combination ofOxaliplatin, retitrexel and irinotecan. The results showed that more patients with the combination of retitrexel and irinotecan would have disease progression, and the difference

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was statistically significant (56.67% vs 30.00%, P < 0.05);Oxaliplatin combined with letitrexed and irinotecan had a higher objective remission rate and disease control rate, and the difference was statistically significant (40.00% vs 16.67%, P < 0.05; 70.00% vs 43.33%, P < 0.05);Oxaliplatin combined with retitrexed and irinotecan could prolong the median PFS and OS, and the difference was statistically significant (5 vs 8 months, P < 0.05; 11 vs 14, P < 0.05).

In this study, the two groups had obvious toxic and side effects such as bone marrow suppression, nausea and vomiting, fatigue and abnormal transaminase, and grade I-II toxic and side effects were more serious [19,20]. Among them, the incidence of neutropenia and grade I-II toxic and side effects of nausea and vomiting in the triple regimen ofOxaliplatin combined with letitrexed and irinotecan was higher than that of letitrexed and irinotecan, and the difference was statistically significant (46.67% vs 20.00%, P < 0.05; 43.33% vs 16.67%, P < 0.05), but it can be effectively alleviated and accepted after symptomatic treatment.

Bevacizumab combined with letitrexed and irinotecan can receive higher Orr and DCR in the failed treatment of first-line fluorouracil combined with oxaliplatin in elderly patients with advanced liver cancer, and can prolong the PFS and OS of patients. Although the incidence of grade I-II toxic and side effects of neutropenia and malignant vomiting is high, it is acceptable. Therefore, we recommend it as a second-line treatment for elderly patients with advanced liver cancer, which should be popularized and applied in clinic.

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