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Original Research Article

Comparison of capecitabine and tegafur/gimeracil/oteracil (S-1) in the treatment of advanced breast carcinoma in the elderly

Dong-Xing Zheng[1]*, Ji-Hai Jin[2], Yu-Juan Liu[3]
[1]Oncology Department II, [2]Breast Surgery, [3]Department of Pediatrics, Binzhou People's Hospital, Binzhou, Shandong, 256600, PR China

For correspondence: **Email: zhengdx5566@163.com*

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Abstract

Purpose: *To analyse and compare the clinical effects and safety of capecitabine and tegafur/gimeracil/oteracil (S-1) in the treatment of advanced breast carcinoma.*
Methods: *Eighty-four metastatic breast cancer elderly patients for whom first or second-line treatment had failed, were selected from among those admitted to the oncology ward of Binjiang People's Hospital, China between January 2014 and June 2015. They were randomly divided into S-1 group (n = 41) and capecitabine group (n = 41) and received varying doses of those drugs according to body surface area. Clinical effects, progression-free survival, and incidence of adverse reactions were compared for the two groups following treatment.*
Results: *Disease control rate (CR) in S-1 group was 55.6 %, much higher than 35.1 % observed for capecitabine group ($p < 0.05$). The disease control rate for the S-1 group was 93.7 %, also much higher than the 70.6 % found in capecitabine group. Survival analysis showed that the median survival times of the two groups did not differ significantly ($p > 0.05$). Furthermore, some adverse reactions such as myelosuppression and lack of strength, did not differ significantly between the two groups ($p > 0.05$), whereas others, including leukopenia, nausea and vomiting and hand-foot syndrome were more serious and frequent in capecitabine group than in S-1 group ($p < 0.05$).*
Conclusion: *Monotherapy with S-1 is more effective than that with capecitabine. Adverse reactions are minimal for both drugs.*

Keywords: *Breast carcinoma, Capecitabine, S-1, Adverse reactions, Myelosuppression, Leukopenia, Hand-foot syndrome*

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INTRODUCTION

Since the 1980s, breast cancer has had the highest incidence and the sixth-highest mortality rate of all malignant tumours in women. In many cases, these cancers have already progressed to a late stage, some with distant metastases, by the time of initial diagnosis [1,2]. Surgery and chemotherapy are the major treatment methods for breast cancer. To extend survival as much as possible, chemotherapy without surgical treatment is more appropriate for late-stage

breast cancer [3,4]. The most preferred chemotherapeutic drugs are anthracyclines and taxanes, but their toxicity and side effects can severely reduce treatment effectiveness andquality of life for elderly patients most such patients are intolerant of combined chemotherapy. Many patients with advanced breast cancer have already experienced treatment failure using the drugs mentioned above. Currently, effective, safe and easy-to-administer therapeutic regimens that can be maintained over the long term are lacking in clinics.

Drugs related to 5-fluorouracil (5-FU) are effective in the treatment of breast cancer. Oral administration of capecitabine is recommended as a standard salvage treatment although adverse reactions such as hand-foot syndrome and gastrointestinal side effects restrict its clinical application [5,6]. Some studies [7,8] have demonstrated significant effects achieved after a single treatment with S-1, with minimal adverse reactions. However most of the research data are from Japan, and few studies have been performed in China. This study sought to compare the curative effects and safety of S-1 and capecitabine in the treatment of patients with advanced breast cancer.

METHODS

Subjects

Eighty-two elderly patients with advanced breast cancer admitted to Binzhou People's Hospital, China, between January 2014 and June 2015, were selected. All cases were confirmed as advanced breast cancer, with biopsy-proven invasive ductal carcinomas and distant metastases observed by Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). The subjects were all females aged from 63 to 81 years (median 51 years). All patients were observed to have tumour progression after one or two regimens of chemotherapy. Patients were included if they had measurable lesions according to the response evaluation criteria in solid tumours (RECIST) (version 1.1) [9], and were predicted to have at least a further 6months of survival, with good bone marrow, hepatic, and renal function. Those with rapid disease progression, contraindications to chemotherapy, organ risks, liver and kidney function deficiency, or uncontrolled cerebral metastasis were excluded. The study was approved by the Medical Ethics Committee of Binzhou People's Hospital (approval no. BPH20140104ZDX), and the experiment followed the guidelines of the Declaration of Helsinki [10].

Therapeutic regimen

The enrolled patients were separated into an S-1 group and a capecitabine group using a random number table, 41 patients were in each group. Drug doses were set according to the body surface area (BSA) of each patient: 80 mg/day for BSA ≤ 1.25 m^2, 100 mg/day for BSA > 1.25 m^2 but < 1.5 m^2, and 120 mg/day for BSA ≥ 1.5m^2. Patients in the S-1 group received oral S-1 (Shandong New Age Pharmaceutical Co., Ltd., China; State Food and Drug Administration (SFDA) approval number: H20080803) twice daily after breakfast and supper for 28 days, and then stopped taking the drug for 14 days; every 6 weeks was regarded as one cycle. Patients in the capecitabine group received oral capecitabine within 30 min after breakfast and supper for 14 days, and then stopped taking the drug for 7 days; every 3 weeks was regarded as one cycle. Clinical effect was evaluated every 6 weeks. When the effect was evaluated as complete remission (CR), partial remission (PR), or stable disease (SD), treatment was continued until either tumours developed or intolerable adverse reactions appeared.

Observed features and criteria for indexing therapeutic effect

The therapeutic effect was evaluated according to RECIST 1.0. In CR all lesions disappeared and did not recur for 4 weeks. Reduction of lesion areas by more than 30 % and the appearance of no new lesions for 4 weeks was considered PR. An increase in lesion area or the appearance of new lesions was considered progressive disease (PD). All patients were re-examined after two courses of treatment. Lesions were measured before and after treatment and were compared to evaluate clinical effects. The overall response rate (ORR) was the sum of percentages of patients with CR and PR; the disease control rate (DCR) was the sum of percentages of patients with CR, PR and SD. All patients were followed up successfully by telephone and/or by outpatient services. Survival time (in months) were recorded during follow-up and the survival curves were drawn.

Statistical analysis

SPSS software (ver. 12.0; SPSS Inc., USA) was used for statistical analysis. Categorical data were compared between groups using Chi-square tests. Overall survival time was analysed using Kaplan-Meier plots and compared using log-rank tests. Differences were considered statistically significant if $p < 0.05$.

RESULTS

Baseline characteristics and treatment conditions

Of the 82 patients enrolled, 62 (75.6 %) had undergone first-line chemotherapy and 20 (24.4 %) had received second-line chemotherapy. No significant difference was found in general characteristics or previous treatment conditions between the two groups ($p > 0.05$; Table 1).

Clinical efficacy

In S-1 group, the median number of chemotherapy cycles was 3.5 (1 - 11 cycles); after treatment, there were no cases of CR, 13 cases of PR, 14 cases of SD, and 14 cases of PD. In the capecitabine group, the median number of chemotherapy cycles was 4 (1 - 17 cycles); after treatment, there were no cases of CR, 8 cases of PR, 11 cases of SD, and 22 cases of PD.

The ORR of the S-1 and capecitabine groups was 31.7 % (13/41) and 19.5 % (8/41), respectively ($X^2 = 3.963$, $p < 0.05$). The DCR of the two groups was 65.9 % (27/41) and 46.3 % (19/41), respectively ($X^2 = 6.440$, $p < 0.05$). These differences were statistically significant.

Kaplan-Meier analysis indicated that the median progression-free survival (PFS) for the S-1 group and the capecitabine group was 5.5 and 4.5 months, respectively (95 % confidence intervals: 4.7 - 6.3 and 2.4 - 5.6 months); this difference was not statistically significant ($X^2 = 0.219$, $p > 0.05$; Figure 1).

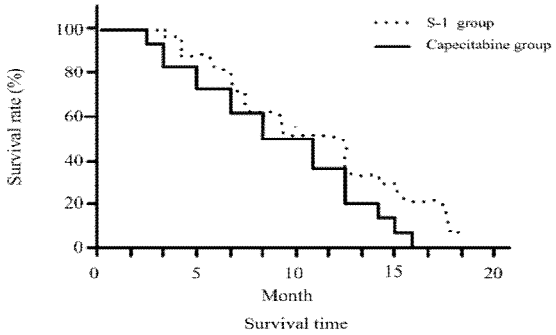

Figure 1: The progression-free survival (PFS) curves of the two groups

Adverse reactions

Some adverse reactions, such as myelosuppression and lack of strength, did not differ significantly between the two groups ($p > 0.05$). Leucopenia, nausea and vomiting, and hand-foot syndrome in the capecitabine group were more serious and more frequent than in the S-1 group ($p < 0.05$; Table 2).

Long-term survival rate

Table 1: Baseline characteristics of the two groups

Clinical pathological parameter		A group (n=41)	B group (n=41)	X^2	*P*
Median age (years)		69.4±5.6	70.1±5.3		
Molecular subtyping	Luminal A	5(12.2%)	7(17.1%)		
	Luminal B	16(39.0%)	18(43.9%)		
HER2 overexpression		9(22.0%)	10(24.4%)	1.927	>0.05
Triple negative		11(26.8%)	6(14.6%)		
Menstrual state	Non-menopausal	13(31.7%)	17(41.5%)	1.078	>0.05
	Post-menopausal	28(68.3%)	24(58.5%)		
Number of metastatic lesions (n)	1	12(29.3%)	9(22.0%)	1.372	>0.05
	2-3	21(51.2%)	24(58.5%)		
	≥4	8(19.5%)	8(19.5%)		
History of pulmonary metastasis	With	22(53.7%)	24(58.5%)	0.158	>0.05
	Without	19(46.3%)	17(41.5%)		
History of liver metastasis	With	25(61.0%)	20(48.8%)	1.267	>0.05
	Without	16(39.0%)	21(51.2%)		
Chemotherapy cycle number (n)	1	27(65.9%)	31(75.6%)	1.178	>0.05
	2	14(34.1%)	10(24.4%)		
Salvage chemotherapy with anthracyclines	With	23(56.1%)	19(46.3%)	0.016	>0.05
	Without	18(43.9%)	22(53.7%)		
Salvage chemotherapy with taxanes	With	34(82.9%)	30(73.2%)	2.217	>0.05
	Without	7(17.1%)	11(26.8%)		
Salvage chemotherapy with platinum	With	20(48.8%)	22(53.7%)	1.305	>0.05
	Without	21(51.2%)	19(46.3%)		

Note: A group: S-1 group; B group: Capecitabine group; HER2: human epidermal growth factor receptor 2

Table 2: Incidence of adverse reactions between the two groups (N, %)

Group	A group	B group	X^2	*p*
Myelosuppression	14(34.1%)	13(31.7%)	0.027	>0.05
Lack of strength	29(70.7%)	32(78.4%)	0.051	>0.05
Leukopenia	10(24.4%)	28(68.3%)	7.648	<0.05
Nausea and vomiting	14(34.1%)	39(95.1%)	4.847	<0.05
Hand-foot syndrome	9(22.0%)	30(73.2%)	5.906	<0.05

Note: A group = S-1 group; B group = capecitabine group

DISCUSSION

Breast cancer usually becomes metastatic at an advanced stage, at which point it is difficult to treat. Surgical treatment that is suitable at an early stage is not applicable in late-stage disease. The wide distribution of lesions and their significant invasion of surrounding tissues mean that surgery cannot effectively remove them. Therefore, palliative treatment is frequently used for patients with advanced breast cancer, with the intention of extending survival time [11]. Many guidelines recommend single-agent sequential chemotherapy as the first choice for patients with metastatic breast cancer. Although combination chemotherapy may result in higher RRs and longer PFS, it does not confer a survival advantage, and the incidence of toxicity and side effects is significantly increased [12]. Single-agent sequential chemotherapy is thus more beneficial in terms of quality of life. A human pharmacodynamics study [13] suggested that capecitabine, which can be absorbed well, generated a significantly higher concentration of fluorouracil in tumour tissues than in adjacent normal tissues. A study by Ershler WB [14] demonstrated that capecitabine could exert an objective effect on advanced breast cancer and was, moreover, effective and safe. While toxic reactions to capecitabine were controllable in the treatment of weakened patients with advanced breast cancer, there was a high risk of renal function impairment in the elderly [14]. Another study [15] enrolled 236 patients with advanced breast cancer previously treated with anthracyclines and taxanes, and treated them with capecitabine; the RR and median PFS were 23.3 % and 4.7 months, respectively, and remission was sustained in patients with oestrogen receptor-positive cancers and single metastatic lesions . In the present study, the RR of the capecitabine group was 19.5 %, and the median PFS was 4.5 months, suggesting good tolerance that was consistent with previous research results. S-1, a fluorouracil-based anticancer drug composed of tegafur, gimeracil, and oteracil potassium, can effectively inhibit dihydropyrimidine dehydrogenase and extend the duration of effective 5-FU concentrations in tumour tissues and surrounding blood. Oteracil potassium can selectively inhibit the activity of 5-FU metabolic enzymes, reduce the phosphorylation of 5-FU, and lessen its toxic effects in the digestive tract. Compared to capecitabine, S-1 can maintain higher plasma drug concentrations, improve anticancer activity, significantly reduce toxicity, and be administrated conveniently. A Japanese phase II clinical study [16] verified the efficacy and safety of S-1 in the treatment of breast cancer. In that study, 108 patients with advanced breast cancer resistant to taxol were treated with S-1; the RR and median survival time was 41.7 % and 872 d, respectively; grade III - IV toxic reactions included leukopenia (9.1 %), fatigue (2.7 %) and poor appetite (3.6 %), yielding S-1 a high safety rating.

Yuan *et al* [17] carried out a phase II clinical study on 33 patients for whom previous treatment with taxanes and anthracyclines and had failed. As second-line mono-chemotherapy, the median PFS and RR with S-1 were 3.3 months and 33.3 %, respectively. The present study found a CR rate for S-1 group of 31.7 %, which was much higher than the 19.5 % seen in the capecitabine group; the overall DCR of the S-1 group was 65.9%, much higher than the 46.3 % seen with capecitabine. Some adverse reactions, such as leukopenia, nausea and vomiting, and hand-foot syndrome were more serious in capecitabine group than in S-1 group ($p < 0.05$).

Limitation of the study

The number of cases enrolled in the study was small, and the observation time was not long. Hence, longer studies with a larger sample size are required to further investigate the clinical effects of capecitabine and S-1.

CONCLUSION

The findings of this study indicate that S-1 has a higher efficacy than capecitabine, and also that it induced minimal toxicity and side reactions in advanced breast cancer patients for whom previous treatment with anthracyclines and taxanes failed. Therefore, S-1 seems a better choice than capecitabine in the clinical treatment of advanced breast cancer.

DECLARATIONS

Conflict of Interest

The authors declare that no conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Dong-Xing Zheng and Ji-Hai Jin: Study design, data collection and analysis. Ji-Hai Jin and Yu-Juan Liu: Manuscript preparation, drafting and revising. Dong-Xing Zheng: Review and final approval of manuscript.

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