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Observation of efficacy and prognosis of chemoradiotherapy with apatinib in combination with oxaliplatin + 5-fluorouracil + leucovorin in the gastric cancer in advanced stage

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► ***Original article***

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ABSTRACT

Background: To investigate the clinical efficacy of apatinib in combination with oxaliplatin + 5-fluorouracil + leucovorin in clinical chemotherapy for the advanced gastric cancer. ***Materials and Methods:*** Between June 2016 and December 2018, we enrolled a total of 92 patients with advanced gastric cancer who were receiving 4500 cGy of radiation through the 5 weeks after resection of adenocarcinoma, and divided them into two groups as per the treatment strategies, with 46 patients in each group. Patients in the control group underwent the regular chemotherapy (oxaliplatin + 5-fluorouracil + leucovorin), while those in the observation group would additionally receive the medication of apatinib. We compared the efficacy, changes in the levels of high-sensitivity C-reactive protein (hs-CRP) and Tumor necrosis factor (TNF-α) in serum, prognosis and adverse reactions between two groups, or before and after treatment. ***Results:*** In the observation group, the total effectiveness rate was higher than that in the control group. Also, after treatment, significant decreases were found in levels of high-sensitivity C-reactive protein and TNF-α in serum of patients in the observation group, more evident than those in the control group. Moreover, progression-free survival and total survival durations of patients were significantly longer than those in the control group, while the incidence rate of adverse reaction was reduced sharply (all $P < 0.05$). ***Conclusion:*** our study showed that apatinib combination with oxaliplatin + 5-fluorouracil + leucovorin seems to have promising efficacy, and is worthy of being studied as a new regimen of gastric cancer treatment.

Keywords: *Apatinib, oxaliplatin + 5-fluorouracil + leucovorin, chemotherapy, advanced gastric cancer, efficacy, prognosis.*

INTRODUCTION

Gastric cancer, as the common malignant tumors in digestive system, is frequently found in the gastric mucosal epithelial tissues, usually caused by the alteration of dietary structure, infection of *H pylori* or life pressure, with clinical manifestations, including anemia, malnutrition or emaciation [1, 2]. Gastric cancer is also one of the malignant tumors with a higher prevalence and mortality rate in the gastrointestinal tract, ranking second in all tumor-resulted death. Advanced gastric cancer, due to the loss of opportunity for radical surgery, or the susceptibility of recurrence or metastasis after early-stage operation, is only managed by the

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chemotherapy or radiotherapy, so as to prolong the survival of patients [3]. However, chemotherapeutics is frequently limited in clinical application due to its toxic effect, tremendous consumption and poor tolerance to the drugs [4]. Apatinib, a small-molecule tyrosine kinase inhibitor (TKI), can inhibit the vascular endothelial growth factor receptor 2 (VEGFR-2) by binding to VEGFR-2 selectively to reduce the proliferation and migration of endothelial cells, and the density of the microvessel inside tumors, thereby suppressing tumor growth [5]. Local recurrence in the bed of a surgical tumor along with recurrence in the lymph nodes or metastasis to distant areas are almost identical causes of recurrence in patients with gastric cancer [6].

In a study, concurrent apatinib and local radiation therapy was used advanced gastric cancer and revealed that if chemotherapy is not well effective, some patients with advanced gastric cancer can gain from combined apatinib with local radiation therapy [7].

In previous studies 5-fluorouracil, low-dose leucovorin, and oxaliplatin have been used as a specific treatment regimen of gastric cancer, known as the FLOX regimen [8]. In Wang *et al.*, study, apatinib was used for gastric cancer treatment in dose of 250 to 850 mg. their study showed significant increased overall survival in lower-doses [9].

Various studies with different treatment regimens have been implicated to help lengthen overall survival of gastric cancer patients; while no previous study has combined apatinib with FLOX regimen (5-fluorouracil + leucovorin + oxaliplatin). In this study, we analyzed the clinical efficacy of apatinib in combination with oxaliplatin + 5-fluorouracil + leucovorin on the advanced gastric cancer, and gained the following results.

MATERIALS AND METHODS

General data

Between June 2016 and December 2018, a total of 92 advanced gastric cancer patients were recruited into this study as the subjects, and divided into two groups randomly, the control group and the observation group, with 46 patients in each group. Inclusion criteria: 1) Patients with the diagnosis of advanced gastric cancer confirmed by the pathological examination; 2) Patients with no contraindication of chemotherapy; 3) Patients who were not available for surgical treatment; 4) Patients with an expected survival time > 3 months; 5) Patients themselves or their family agreeing to participate in the study after they were informed of the content of the study; 6) this study had been reviewed and approved by the Ethical Committee of Linyi Central Hospital. Exclusion criteria: 1) Patients that did not conform to the criteria above; 2) Patients with the history of palliative chemotherapy; 3) Patients in lactate period or pregnancy.

Patients in both groups received 4500 cGy of radiation to the tumor site, 2 cm beyond the resection margins, in 25 fractions, five days per week using megavoltage equipment (Theratron 780E Cobalt Radiotherapy; MDS Canada Inc. DBA MDS Nordion).

Patients in the control group received the regular chemotherapy as follow: intravenous infusion of oxaliplatin [Hangzhou Sanofi-Aventis Pharmaceutics Co., Ltd (Distributed in Belgium and China); Registration No.: H2009117; Specification: 50 mg] + 5-fluorouracil (Hainan Chuntch Pharmaceutical Co., Ltd; SFDA No.: H20051626; Specification: 0.25 g calculated by the fluorouracil) + leucovorin (Henan Furen Huaiqingtang Pharmaceutical Co., Ltd; SFDA No.: H20084204; Specification: 25 mg). For dosage, 5 -fluoroucil was given at frequency of 6 h/d, 400 mg/(m^2·d), once per day for 4 days; oxaliplatin at 130 mg/m^2 + 5% 500 mL glucose solution for intravenous infusion for 4 hours; leucovorin at 200 mg/m^2 for intravenous infusion for longer than 3 min.

On the basis of the regular chemotherapy, patients in the observation group additionally took apatinib (Jiangsu Hengrui Pharmaceutical Co., Ltd; SFDA No.: H20140105; 0.425 g × 7 tablets × 2 plates; 0.25 g × 10 tablets) orally at dose of 850 mg, once per day. For two groups, treatment lasted for 4 courses, one course consisting of 3 weeks.

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Observation group

Efficacy

Efficacy was evaluated as per the Response Evaluation Criteria In Solid Tumors (RECIST): Complete remission (CR): Recovery ≥75% or higher in clinical symptoms after treatment; Partial remission (PR): Recovery between 50% and 75% in clinical symptoms after treatment; Stable disease (SD): Recovery <50% in clinical symptoms after treatment, but no emergence of new lesions; progressive disease (PD): No obvious recovery after treatment, or even deterioration in some patients. The total effectiveness rate = Rate of CR + Rate of PR.

Levels of hs-CRP, CSF and TNF-α in serum [6]

Measurements of hs-CRP, CSF and TNF-α in serum were performed before treatment and after 1 week of treatment. Prior to the measurement, patients were required to keep fasting for 8 h, and in the next morning, 6 mL fasting elbow venous blood was collected and incubated with 50 U/mL heparin for anti-coagulation to isolate the monocytes that were preserved at -80°C. TNF-α level was measured by the Enzyme-linked immunosorbent assay (ELISA).

Prognosis

Prognosis was compared mainly through the progression-free survival time and total survival time of patients between two groups.

Adverse reactions

The incidence rates of anemia, diarrhea, thrombocytopenia, nausea and vomiting, and leukopenia were analyzed in patients of two groups.

Statistical methods

All data were analyzed and processed by use of the statistical software SPSS 23.0. Enumeration data were expressed in form of rate (%), and compared by use of chi-square test; measurement data were expressed in form of mean ± standard deviation, and compared by use of *t* test. P>0.05 suggested that the difference had no statistical significance.

RESULTS

In the observation group, there were 29 males and 17 females, aged between 34 and 78 years old, with an average of (52.46±13.47) years; as per the scoring criteria of Eastern Collaborative Oncology Group (ECOG), there were 38 patients scoring between 0 and 1 point and 8 scoring 2 points; for tissue differentiation, there were 4 patients in well differentiation, 22 in moderate differentiation and 20 in poor differentiation. In the control group, there were 30 males and 16 females, aged between 33 and 79 years old, with an average of (52.71±13.62) years; as per the scoring criteria of Eastern Collaborative Oncology Group (ECOG), there were 41 patients scoring between 0 and 1 point and 5 scoring 2 points; for tissue differentiation, there were 5 patients in well differentiation, 24 in moderate differentiation and 17 in poor differentiation. Comparison of the general data between two groups revealed no significant differences (P=0.05), suggesting that data were comparable. Comparison of the clinical efficacy between two groups.

In the observation group, the total effectiveness rate was higher than that in the control group (χ^2=5.2629, P<0.05; table 2).

The levels of hs-CRP, CSF and TNF-α in serum before and after treatment

Also, after treatment, significant decreases were found in levels of hs-CRP, CSF and TNF-α in serum of patients in the observation group, more evident than those in the control group (P<0.05; table 3).

Comparison of the prognosis between two groups

Moreover, progression-free survival and total survival durations of patients were significantly longer than those in the control group (P<0.05; table 4).

Comparison of the adverse reactions between two groups

The incidence rate of adverse reactions in the observation group was 12.9%, significantly lower than 43.5% in the control group (χ^2=5.1726, P<0.05; table 5).

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Table 1. Demographic information of patients.

Group	Total	Male/Female n	Age Mean ±SD	ECOG Status (0&1/2)	Tumor Differentiation n		
					Well differentiated	Moderate differentiated	Poor differentiated
Observation group	46	29/17	52.46±13.47	38/8	4	22	20
Control group	46	30/16	52.71±13.62	41/5	5	24	17
P	-	>0.05	>0.05	>0.05	>0.05		

Table 2. Comparison of the efficacy between two groups [n (%)].

Group	N	CR	PR	SD	PD	Total effectiveness rate (%)
Observation group	46	11(23.91)	23(50.00)	8(17.39)	4(8.7)	73.91
Control group	46	6(13.05)	11(23.91)	22(47.83)	7(15.21)	36.96

Table 3. Comparison of the levels of hs-CRP, CSF and TNF-α in serum before and after treatment in two groups (mean ± standard deviation).

Group	hs-CRP (mg/L)		CSF (pg/mL)		TNF-α (g/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	23.54±4.11	11.87±1.21	36.24±15.13	15.15±9.11	29.34±8.13	18.35±5.21
Control group	22.46±4.13	15.43±2.11	36.57±16.25	23.43±11.13	29.43±9.24	25.46±6.21
t	0.9068	7.1303	0.0728	2.8175	0.0358	4.2896
P	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Table 4. Comparison of the progression-free survival time and total survival time between two groups (mean±standard deviation, months).

Group	N	Progression-free survival time	Total survival time
Observation group	46	5.38±2.86	9.03±3.84
Control group	46	3.37±2.47	7.16±2.04
t		2.6153	2.1133
P		<0.05	<0.05

Table 5. Comparison of the incidence of adverse reactions between two groups [n (%)].

Group	N	Anemia	Diarrhea	Thrombocytopenia	Nausea and vomiting	Leukopenia	Total
Observation group	46	2(4.3)	2(4.3)	0(0)	2(4.3)	0(0)	6(12.9)
Control group	46	6(13.0)	4(8.7)	2(4.3)	6(13.0)	2(4.3)	20(43.5)

DISCUSSION

With the continuous development in marketing economy and tremendous change in life style, people have experienced magnificent variation in the diet structure, which, plus the huge pressure of work, results in the continuous increase in the prevalence of gastric cancer. Accumulating evidence has shown that various factors in gastric cancer are prone to the younger people; moreover, patients in early stage of gastric cancer usually report no evident symptoms, only manifesting the accidental discomfort in the upper abdomen, generally progressing into the clinical symptoms including nausea and vomiting, similar to the gastric ulcer and chronic gastritis, which are frequently ignored or misdiagnosed [10, 11]. Gastric cancer,

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once progressed into the progressive stage, manifests the weight loss and pains in varying degrees, and fatigue in the majority of patients, which become more frequent and severe in the advanced stage, including emaciation, anemia and malnutrition. Surgical treatment is preferred in patients in early stage and progressive stage, so as to achieve the goal of elimination and mitigate the clinical symptoms and the pains. In advanced stage, chemotherapy is mainly applied as the major method to prolong the life, or the combination of chemotherapeutics and targeted drugs [12] can target the cancer cells, thus mitigating the damage to the normal cells.

Oxaliplatin, as the 3rd generation platin-based anti-cancer drugs, is a kind of DACH-platin compound that, with fluorouracil, is suitable for the treatment of colorectal cancer, gastric cancer and non-small cell lung cancer [13]. Fluorouracil is the mostly used anti-tumor drugs currently, and as a cycle-specific drug, it can interfere on the DNA synthesis by decreasing the activity of thymidylate synthase [14]. Apatinib, a small-molecule VEGFR TKI, is the only oral preparation developed for the treatment of advanced gastric cancer among all targeted drugs that can block the phosphorylation pathway and transduction of downstream signals through specifically binding to the intracellular ATP, thereby suppressing the angiogenesis in tumor tissues. Thus, apatinib has served as the typical third-line drugs or above in treatment of advanced gastric cancer [15].

In this study, we investigated the clinical efficacy of regular chemotherapy in combination with apatinib in treatment of advanced gastric cancer patients, and found that this strategy gained promising outcome, with a total effectiveness rate of as high as 73.91%. After treatment, levels of hsCRP, CSF and TNF-α were decreased evidently, while the progression-free survival time and total survival time were prolonged. Overall, the incidence rate was decreased to 12.9%, significantly than 43.5% of those that only received the chemotherapy, similar to the results of Xue *et al.* [17].

Due to the high rate of local recurrences after surgery, radiotherapy in the treatment of gastric cancer was considered to reduce the recurrence rate. Clinically, if radiotherapy is not performed and only surgery is performed, the local recurrence rate will be at least 25%. Some surgeons tried to reduce local recurrence by increasing the size of surgery, such as omentum removal, spleen (splenectomy), or lymphatic dissection (D2), but these extensive surgeries were not very successful in increasing the patient's survival and local control [18, 19].

Targeted treatment for gastric cancer has become a hot spot in clinical research, and apatinib is the first oral preparation that antagonizes the angiogenesis in advanced gastric cancer, with the promising clinical efficacy. For patients that tolerate the treatment well, the sufficient initial dose can improve the efficacy of apatinib [20]. Therefore, in clinical chemotherapy for advanced gastric cancer, administration of apatinib in combination with oxaliplatin + 5-fluorouracil + leucovorin gains promising efficacy, and is worthy of being promoted.

To compare the effectiveness of these therapies, some large studies have been performed so far. In the largest study, known as Adjuvant chemoradiation therapy in stomach cancer (ARTIST), 458 patients with gastric cancer who underwent complete gastrectomy (complete gastric resection) and lymphatic D2 dissection were studied in two groups. In the first group, patients received only 6 courses of chemotherapy with capecitabine and cisplatin. Chemotherapy did not significantly reduce the recurrence but the disease-free survival rate increased in the second group [21].

Limitations

This study did not examine the overall survival of patients. Since patients with or without lymph nodes involved in our study were not isolated and this may be a major problem that we recommend further studies to investigate it.

CONCLUSION

In clinical chemoradiotherapy for advanced

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gastric cancer, administration of apatinib in combination with oxaliplatin + 5-fluorouracil + leucovorin gains promising efficacy, and is worthy of being promoted in a long-term study evaluating the local recurrence.

***Conflicts of interest*:** *Declared none.*

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