Tropical Journal of Pharmaceutical Research June 2022; 21 (6): 1335-1340
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i6.29

Original Research Article

Effect of oteracil in combination with gimeracil on long-term survival and postoperative complications in elderly patients undergoing radical surgery for biliary tract cancer

Xiaona Zhang, Tingting Zhang, Wenliang Wu, Peng Tang*
Department of Surgical Oncology, Changle People's Hospital, Weifang 262400, Shandong Province, China

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

Sent for review: 30 December 2021 *Revised accepted: 30 May 2022*

Abstract

Purpose: *To investigate the effect of oteracil (Oxo) in combination with gimeracil (CDHP) on long-term survival and postoperative complications in elderly patients undergoing radical surgery for biliary tract cancer (BTC).*
Methods: *Clinical data for 70 patients who underwent radical surgery for BTC in the Oncology Department of the Changle People's Hospital, Weifang, China from April 2017 to April 2018 were collected. The patients were equally assigned to group A and group B, based on odd or even hospitalization number. After surgery, patients in group A received the combination of Oxo and CDHP, while group B patients received gemcitabine only. Long-term survival and incidence of adverse reactions were compared.*
Results: *Compared with group B, group A had higher total treatment effectiveness ($p < 0.05$), lower clinical indices ($p < 0.05$), lower BPI score ($p < 0.001$) and higher 3-year overall survival ($p < 0.05$).*
Conclusion: *Combined use of oteracil and gimeracil significantly prolongs the survival time and reduce cancer pain in BTC patients, with minimal toxic and side effects. However, further clinical trials are required prior to application in clinical practice.*

Keywords: *Oteracil, Gimeracil, Radical surgery, Biliary tract cancer, Long-term survival, Postoperative complications*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Biliary tract cancer (BTC), a general name for gallbladder cancer and cholangiocarcinoma derived from biliary epithelial cells, is difficult to diagnose at the early stage, and it progresses rapidly [1,2]. Radical surgery for BTC is a common method used in the treatment of the disease, but most patients miss the best treatment opportunity due to late diagnosis. Patients with metastatic or recurrent BTC can only receive chemotherapy or comprehensive therapy, but this does not result in any significant clinical effects. For BTC patients undergoing surgical treatment, the use of anticancer drugs after surgery is of great significance for prolonging the survival rate and inhibiting progression of disease [3]. At present, radical surgery for BTC has made great impact, but

research on postoperative consolidation therapy is relatively scarce. The efficacies of commonly used postoperative consolidation therapy drugs such as adriamycin and oxaliplatin have been confirmed, but their clinical applications are relatively limited due to serious toxic and side effects [4,5].

Cancer research has revealed that tegafur, gimeracil and oteracil potassium effectively reduce the side effects of surgery in patients. In particular, gimeracil (CDHP) is one anticancer drug that inhibits the toxic and side effects of the antitumor drug tegafur (FT). Apart from effectively suppressing the decomposition of fluorouracil, CDHP is associated with prolonged exposure time and enhanced antitumor efficacy, as have been confirmed in the treatment of advanced gastric cancer [6]. So far, not much is known on the effect of combined use of Oxo and CDHP on long-term survival and postoperative complications of patients after radical surgery for BTC. Therefore, this study was aimed at investigating the effect of Oxo-CDHP combination treatment on BTC patients.

METHODS

General profile of patients

Clinical data for 70 selected patients undergoing radical surgery for BTC in the Oncology Department of Changle People's Hospital, Weifang, China from April 2017-April 2018, were collected. The patients were randomly assigned to two groups (A and B). There were no obvious differences in baseline data between the two groups ($p > 0.05$), as shown in Table 1.

Inclusion and exclusion criteria

Exclusion criteria

Patients in the following categories were included in this study: patients aged 60 years old or above, patients meeting the indications of radical surgery for BTC, and those with expected survival time not less than 3 months.

Table 1: Comparison of baseline data

Parameter	Group A (n=35)	Group B (n=35)	χ^2/t	*P*-value
Gender				
Male	19(54.29%)	20(57.14%)	0.058	0.810
Female	16(45.71%)	15(42.86%)		
Age (mean ± SD) (years)	66.24±4.36	66.38±4.29	0.135	0.893
BMI (kg/m^2)	22.18±1.35	22.21±1.39	0.092	0.927
Maximum diameter of the lesion (cm)	3.52±1.46	3.56±1.52	0.112	0.911
Tumor type				
Gallbladder tumor	18(51.43%)	21(60.00%)	0.521	0.470
Bile duct tumor	17(48.57%)	14(40.00%)		
TNM stage				
II	7(20.00%)	9(25.71%)	0.324	0.569
III	13(37.14%)	12(34.29%)	0.062	0.803
IV	15(42.86%)	14(40.00%)	0.059	0.808
Pathological grade of carcinoma				
Poorly differentiated	10(28.57%)	14(40.00%)	1.015	0.314
Moderately differentiated	16(45.71%)	14(40.00%)	0.233	0.629
Highly differentiated	9(25.71%)	7(20.00%)	0.324	0.569
Basic disease				
Hypertension	24(68.57%)	21(60.00%)	0.560	0.454
Diabetes mellitus	14(40.00%)	15(42.86%)	0.059	0.808
Heart disease	15(42.86%)	16(45.71%)	0.058	0.810
Coronary heart disease	16(45.71%)	18(51.43%)	0.229	0.632
Location of residence				
Cities and towns	14(40.00%)	16(45.71%)	0.233	0.629
Countryside	21(60.00%)	19(54.29%)		

Exclusion criteria

Patients who had received chemotherapy and radiotherapy before surgery, patients with other malignant tumors, those who had severe hematological, gastrointestinal and cardiopulmonary diseases, patients who were allergic to the drugs used, and those who dropped out of the study, were excluded. This study received the approval of the Ethics Committee of Changle People's Hospital (approval no. 20170202), and was conducted in line with the guidelines of Declaration of Helsinki (as revised in 2013) [7]. Written and signed informed consent was obtained from the patients and/or guardians.

Patient handling

All patients underwent radical surgery for BTC. Patients were kept in spread-eagled position after general anesthesia, with the position adjusted based on the tumor type and location so as to facilitate surgery [8-10]. Patients in group A were treated with Oxo plus CDHP after surgery, and orally administered tegafur, gimeracil and oteracil potassium capsules (NMPA approval no. H20080802; Shandong New Time Pharmaceutical Co. Ltd; Specification: 25 mg x 36 capsules per sachet) twice a day (40 - 60 mg at a time). After surgery, patients in group B were treated with gemcitabine (NMPA approval no. H20103522; Beijing Union Pharmaceutical factory; Specification: 1 g) at a dose of 1000 mg/m^2 via intravenous infusion, once daily, with each infusion time less than 30 min. In both groups, treatment cycle lasted for 21 days, with continuous treatment for 2 cycles. The patients' disease conditions were monitored during therapy. In the event of tumor progression and severe adverse reactions, the treatment was discontinued and the treatment plan was re-adjusted according to the patients' condition.

Evaluation of indices/parameters

Treatment efficacy was evaluated in both groups based on the evaluation criteria in the latest version of *Guidelines for Diagnosis and Treatment of Biliary Tract Cancer by Chinese Society of Clinical Oncology (CSCO)* [11]. Treatment efficacy was divided into *complete response* (disappearance of focal lesions and short diameter of pathological lymph node, i.e, < 10 mm, without new lesions); *partial response* (sum of lesion diameters decreased by ≥ 30 %, without new lesions); *stable disease* (sum of lesion diameters decreased by < 30 %, or increased by < 20 %), and *progressive disease* (sum of lesion diameters increased by ≥ 20 %, or the appearance of new lesions).

DCR = (CR + PR + SD)/T x 100 …… (1)

where DCR = disease control rate; CR = number of patients with complete response; PR = number of patients with partial response; SD = stable disease, T = total number of cases.

Clinical indicators

After therapy, fasting venous blood (5 mL) was taken from each patient in both groups, for assay of levels of aspartate transaminase (AST) and alanine transaminase (ALT). Carcinoembryonic antigen (CEA) level was determined using radioimmunoassay method. Carbohydrate antigen 125 (CA125) was measured using electrochemical immunoassay (ECLIA) method, while carbohydrate antigen 153 (CA153) was assayed with magnetic homogeneous chemiluminescence immunoassay method. Albumin (ALB) level was measured with Automatic Biochemical Analyzer (Nanjing Vedeng Medical Co. Ltd.; Product model: BS-280).

Evaluation of cancer pain

Cancer pain in patients was evaluated using Brief Pain Inventory (BPI) [12]. This comprised 7 dimensions with 70 points in total. A higher score represented more severe cancer pain. Telephone and outpatient follow-ups were applied to ascertain the 3-year survival time of each patient. Routine blood test, and liver and kidney function tests were used to check the incidence of clinical complications in patients at 6 months after the end of therapy.

Statistical analysis

The experimental data were statistically analyzed and processed with SPSS 21.0, while selected graphics were prepared with GraphPad Prism 7 (GraphPad Software, San Diego, USA). Count data are expressed as numbers and percentages; n (%), and were analyzed using chi squared (χ^2) test. Measurement data are presented as mean ± SD, and were compared using *t*-test. Statistical significance at $p < 0.05$.

RESULTS

Treatment effectiveness

The total treatment effectiveness was higher in group A than in group B ($p < 0.05$), as shown in Table 2.

Table 2: Comparison of clinical efficiency (n (%))

Group	CR	PR	SD	PD	DCR
A	18 (51.43%)	9 (25.71%)	7 (20.00%)	1 (2.86%)	97.14% (34/35)
B	5 (14.29%)	8 (22.86%)	16 (45.71%)	6 (17.14%)	82.86% (29/35)
χ^2					3.968
P-value					0.046

Table 3: Changes in clinical indexes after therapy (mean ± SD)

Group	CEA (ug/L)	CA125 (U/mL)	CA153 (U/mL)	ALB (g/L)	AST (U/L)	ALT (U/L)
A	8.25±1.76	42.35±3.46	30.51±4.57	56.72±4.71	42.53±4.52	46.71±5.61
B	23.57±4.57	57.81±4.52	53.26±4.18	79.26±5.26	57.89±5.61	53.46±4.78
T	18.507	16.068	21.732	18.886	12.613	5.418
P-value	0.000	0.000	0.000	0.000	0.000	0.000

Table 4: Comparison of incidence of postoperative complications (n (%))

Group	Liver function damage	Stress ulcer bleeding	Decreased platelet count	Anemia	Overall incidence
A	0	0	1 (2.86%)	1 (2.86%)	5.71% (2/35)
B	2 (5.71%)	1 (2.86%)	3 (8.57%)	2 (5.71%)	22.86% (8/35)
χ^2					4.200
P-value					0.040

Changes in clinical indices after therapy

Table 3 demonstrated lower clinical indexes in group A than in group B after therapy ($p < 0.05$).

Post-therapy BPI scores

The BPI score of group A after therapy was lower when compared with group B ($p < 0.001$). These results are shown in Figure 1.

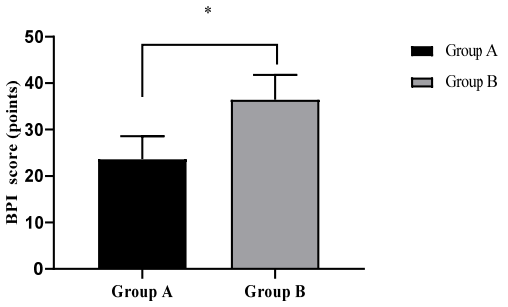

Figure 1: BPI scores after therapy (mean ± SD). *$P < 0.001$, BPI score of group A after therapy vs BPI score of group B after therapy

Long-term survival

The study showed that the median survival time was 23 months in group A and 16 months in group B. The number of survivors was 33 (94.29 %) in group A and 27 (77.14 %) in group B. The 3-year overall survival was markedly higher in group A than in group B ($p < 0.05$). These results are shown in Figure 2.

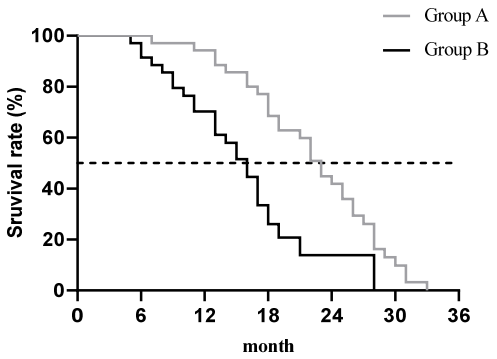

Figure 2: Comparison of long-term survival rates between the two groups

Incidence of postoperative complications

The total incidence of postoperative complications was higher in group A than in group B, as shown in Table 4.

DISCUSSION

Biliary tract cancer (BTC) accounts for about 3 % of digestive system malignant tumors, and it is associated with high malignancy, easy metastasis, poor prognosis and a 5-year survival rate below 5 %. In recent years, with continuous improvements in standards of living and changes

in diets, the incidence of BTC has been on the increase [13]. So far, surgical treatment is still the best way to prolong survival time and achieve good prognosis of BTC patients. A study has shown that some BTC patients still have recurrence after radical surgery, especially those with advanced tumors, incomplete tumor resection and lymph node metastasis, who need adjuvant medical therapy after surgery [14].

Studies on drug treatment of BTC have been ongoing. In recent years, it has been found that some patients benefit from adjuvant medical therapy. Chemotherapy drugs, immunotherapy and targeted therapy which have been proven to produce significant effects in the treatment of other malignant tumors, have also been continuously explored in the treatment of BTC. At present, capecitabine and gemcitabine are commonly used anti-tumor drugs, but they have strong toxic side effects.

Narayan *et al* [15] have reported that patients with advanced gastric cancer treated with capecitabine had numbness of hands and feet, as well as sensational and digestive system abnormalities. These adverse reactions were also confirmed in a study by Hickman *et al* [16]. Tegafur (FT), gimeracil (CDHP) and oteracil potassium (Oxo) are oral anti-cancer agents derived from fluorouracil. Tegafur (FT), the pro-drug of 5-fluorouracil (5-FU), has excellent oral bioavailability, and it is transformed into 5-FU *in vivo*. Gimeracil (CDHP) blocks the degradation of fluorouracil activator, thereby increasing the anti-tumor effect of drugs. Oteracil (Oxo) protects the gastrointestinal mucosa, relieves gastrointestinal reactions during therapy, and it produces good antitumor effect. Tegafur, gimeracil and oteracil potassium promote apoptosis of tumor cells and prolong the survival time of patients, as have been confirmed in the treatment of advanced gastric cancer [17].

In this study, patients with radical surgery for BTC received different drugs in group A (Oxo in combination with CDHP) and group B (gemcitabine). After therapy, the median survival time and overall survival of group A were higher. This finding indicates that the combined therapy effectively prolonged the survival time of patients after radical surgery for BTC. The two treatment regimens caused adverse reactions, with decreased platelet count as the most obvious effect. However, group A had lower incidence of complications. Due to declining immune function and multiple diseases in elderly patients, there is increased risk of adverse reactions after therapy [18,19].

Limitations of the study

Although qualitative, quantitative and comparative analysis were conducted in this retrospective study, there is need for more data on liver function damage and stress ulcer bleeding. In addition, the number of selected cases was relatively small, which is likely to result in bias. Therefore, more multi-center studies with expanded sample size are required to improve the accuracy of the results reported in this research.

CONCLUSION

The combined use of Oxo and CDHP significantly prolongs survival time and reduce cancer pain in patients after radical surgery of BTC, with lower incidence of adverse reactions, when compared with the use of gemcitabine. However, further clinical trials are required prior to adoption this combination in clinical practice.

DECLARATIONS

Conflict of Interest

No conflict of interest 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. Xiaona Zhang and Peng Tang conceived and designed the study, and drafted the manuscript. Xiaona Zhang, Tingting Zhang and Wenliang Wu collected, analyzed and interpreted the experimental data. Tingting Zhang and Peng Tang revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Open Access

REFERENCES

1. Banks A, Coronado G, Zimmerman R, Iyengar G, Holmes DR. Breast conserving surgery with targeted intraoperative radiotherapy for the management of ductal carcinoma in situ. J Surg Oncol 2019; 119(4): 409-420.
2. Bonanno AM, Kiraly LN, Siegel TR, Brasel KJ, Cook MR. Surgical palliative care training in general surgery residency: An educational needs assessment. Am J Surg 2019; 217(5): 928-931.
3. Neuzillet C, Casadei GA, Brieau B, Vivaldi C, Smolenschi C, Brandi G, Tougeron D, Filippi R, Vienot A, Silvestris N, et al Prediction of survival with second-line therapy in biliary tract cancer: Actualisation of the AGEO CT2BIL cohort and European multicentre validations. Eur J Cancer 2019; 111: 94-106.
4. Bagante F, Gani F, Beal EW, Merath K, Chen Q, Dillhoff M, Cloyd J, Pawlik TM. Prognosis and Adherence with the National Comprehensive Cancer Network Guidelines of Patients with Biliary Tract Cancers: an Analysis of the National Cancer Database. J Gastrointest Surg 2019; 23(3): 518-528.
5. Huang X, Yan H, Su Z, Wang J, Zhang J, Zhang X. Clinical efficacy of combination of oxaliplatin and vascular intervention in treatment of advanced cervical cancer and related prognostic factors. Trop J Pharm Res 2022; 21(3): 643-648.
6. Suzuki Y, Kan M, Kimura G, Umemoto K, Watanabe K, Sasaki M, Takahashi H, Hashimoto Y, Imaoka H, Ohno I, et al. Predictive factors of the treatment outcome in patients with advanced biliary tract cancer receiving gemcitabine plus cisplatin as first-line chemotherapy. J Gastroenterol 2019; 54(3): 281-290.
7. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191-2194.
8. Feng FL, Cheng QB, Zhang DD, Li B, Qin H, Xu C, Han M, Yu Y, Li ZZ, Li JY, et al. Targeted deep sequencing contributes to guiding personalized targeted therapy for advanced biliary tract cancer patients with non-radical resection: A real-world study. Oncol Rep 2020; 43: 1089-1102.
9. Weng YC, Jin JB, Huo Z, Shi YS, Jiang Y, Deng XX, Peng CG, Shen BY. Robotic-assisted versus open distal pancreatectomy for benign and low-grade malignant pancreatic tumors: a propensity score-matched study. Surg Endosc 2021; 35: 2255-2264.
10. Shin D, Lee S, Lee JH, Hong SM, Park SY, Yoo C, Lee W, Song KB, Hwang DW, Kim SC, et al. Prognostic implication of high grade biliary intraepithelial neoplasia in bile duct resection margins in patients with resected perihilar cholangiocarcinoma. J Hepatobiliary Pancreat Sci 2020; 27: 604-613.
11. Shroff RT, Kennedy EB, Bachini M, Bekaii-Saab T, Crane C, Edeline J, El-Khoueiry A, Feng M, Katz MHG, Primrose J, et al. Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline. J Clin Oncol 2019; 37(12): 1015-1027.
12. Cheung KWA, Chan PC, Lo SH. The use of ketamine in the management of refractory cancer pain in a palliative care unit. Ann Palliat Med 2020; 9: 4478-4489.
13. Minegaki T, Suzuki A, Mori M, Tsuji S, Yamamoto S, Watanabe A, Tsuzuki T, Tsunoda T, Yamamoto A, Tsujimoto M, et al. Histone deacetylase inhibitors sensitize 5-fluorouracil-resistant MDA-MB-468 breast cancer cells to 5-fluorouracil. Oncol Lett 2018; 16(5): 6202-6208.
14. Kusumoto T, Sunami E, Ota M, Yoshida K, Sakamoto Y, Tomita N, Maeda A, Mochizuki I, Okabe M, Kunieda K, et al. Planned safety analysis of the ACTS-CC 02 trial: A randomized phase III trial of S-1 with oxaliplatin versus tegafur and uracil with leucovorin as adjuvant chemotherapy for high-risk stage III colon cancer. Clin Colorectal Cancer 2018; 17(2): e153-e161.
15. Narayan RR, Creasy JM, Goldman DA, Gönen M, Kandoth C, Kundra R, Solit DB, Askan G, Klimstra DS, Basturk O, et al. Regional differences in gallbladder cancer pathogenesis: Insights from a multi-institutional comparison of tumor mutations. Cancer 2019; 125(4): 575-585.
16. Hickman L, Contreras C. Gallbladder cancer: Diagnosis, surgical management, and adjuvant therapies. Surg Clin North Am 2019; 99(2): 337-355.
17. Tsukita Y, Inoue A, Sugawara S, Kuyama S, Nakagawa T, Harada D, Tanaka H, Watanabe K, Mori Y, Harada T, et al. Phase II study of S-1 in patients with previously treated invasive thymoma and thymic carcinoma: North Japan lung cancer study group trial 1203. Lung Cancer 2020; 139: 89-93
18. Choi SY, Kim JH, Park HJ, Han JK. Preoperative CT findings for prediction of resectability in patients with gallbladder cancer. Eur Radiol 2019; 29(12): 6458-6468.
19. Soeno T, Katoh H, Ishii S, Ushiku H, Hosoda K, Hiki N, Watanabe M, Yamashita K. CD33+ immature myeloid cells critically predict recurrence in advanced gastric cancer. J Surg Res 2020; 245: 552-563.