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ORIGINAL ARTICLE

Advanced duodenal carcinoma: Chemotherapy efficacy and analysis of prognostic factors

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Abstract

Objective This study aimed to determine the efficacy of chemotherapy and to identify potential chemotherapy agents to treat advanced primary duodenal carcinoma (PDC).

Methods Seventy-three patients with advanced PDC were included in the study. Response rate (RR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and prognosis were compared among patients using the Cox proportional hazards model.

Results The overall RR and DCR of 52 patients were 21.15% and 69.23%, respectively. The median PFS and OS times were 4.51 and 11.47 months, respectively. Palliative chemotherapy improved the OS of patients with advanced PDC compared with patients who did not receive chemotherapy (14.28 months vs. 5.20 months, HR = 0.205, 95% CI: 0.077 to 0.547, P = 0.0016). Multivariate analysis indicated mucinous histology and liver metastasis as factors predictive of poor prognosis in patients with advanced PDC.

Conclusion Palliative chemotherapy may improve the OS of patients with advanced PDC. Mucinous histology and liver metastasis were the main prognostic factors in patients with advanced PDC.

Key words: primary duodenal carcinoma (PDC); palliative chemotherapy; survival; prognostic factors

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Primary duodenal carcinoma (PDC) is very rare, accounting for 0.3%–1.0% of gastrointestinal cancers, and 25%–35% of small bowl cancers [1–4]. Epidemiological data indicate that the annual incidence of PDC is 3.7 per million inhabitants in Western countries [5]. Adenocarcinoma of PDC is the most common histological type. Because of the rarity of PDC, no prospective randomized controlled study has evaluated the role of chemotherapy in the treatment of advanced or metastatic PDC and there is no established standard chemotherapy for this disease. Many recent case reports have proven the role of chemotherapy in the treatment of advanced or metastatic PDC. Hadano *et al* from the Department of Surgery, Mazda Hospital, Japan, reported a case of PDC in a patient that responded to chemotherapy with S-1 and irinotecan [6]. Okada *et al* reported a case of liver metastasis associated with PDC that was effectively treated with docetaxel therapy [7]. Yasui *et al* reported a case of recurrent duodenal carcinoma successfully controlled using a FOLFOX regimen [8]. A retrospective small bowel cancer study included a larger number of samples. A retrospective study by Overman *et al* from the M. D. Anderson Cancer Center, USA, reported that chemotherapy with 5-fluorouracil and a platinum compound improved outcomes in patients with metastatic small bowel adenocarcinomas [9]. Another retrospective study by Koo *et al* from the Asan Medical Center, Seoul, Korea, reported palliative chemotherapy may improve survival outcomes in patients with advanced small bowel adenocarcinomas (SBA) including PDC [10].

Patients and methods

Patients and data collection

We identified all patients from the Department of Medical Oncology, Chaoyang Sanhuan Cancer Hospital, Beijing, China, and the Department of Medical Oncology, Cancer Hospital & Institute, Chinese Academy of Medical Sciences & Peking Union Medical College, China, who

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were treated for metastatic PDC between 2002 and 2014. Seventy-three patients with metastatic PDC who had received a histopathologic diagnosis and had radiographically measurable disease (tumor diameter ≥ 10 mm using spiral computed tomography) met the inclusion criteria. Patients who were undergoing first-line chemotherapy for metastatic PDC and who had received ≥ 2 cycles of chemotherapy were included.

Patient medical records were reviewed for information regarding demographic data, tumor characteristics, treatment response, and survival. The tumor stage was determined according to the American Joint Committee on Cancer Staging System. Histologic grading was determined according to the World Health Organization Standard Grading System: poorly differentiated, moderately differentiated, well differentiated, or undifferentiated. Tumors with 2 different degrees of histologic differentiation were recorded as having the lesser grade.

Table 1 Clinical and pathologic tumor characteristics of patients included in the study

Characteristics	No. of patients (%)
Age (year)	
Median	54
Range	31–78
Sex	
Men	47 (64.38)
Women	26 (35.62)
Initial stage	
II–III	41 (56.16)
IV	32 (43.84)
Primary tumor site	
Duodenal bulb	4 (5.48)
Descending	49 (67.12)
Horizontal	4 (5.48)
Ascending	2 (2.74)
Not specified	14 (19.18)
Mucinous histology	11 (15.07)
Histologic grade	
Well differentiated	7 (9.58)
Moderately differentiated	40 (54.79)
Poorly differentiated	14 (19.17)
Undetermined	12 (16.43)
Operation	
Primary tumor resected	44 (60.27)
Surgical bypass	18 (24.66)
Without operation	11 (15.07)
Initial sites of distant metastasis	
Lymph nodes	52 (72.22)
Liver	29 (40.28)
Peritoneum	14 (19.44)
Lung	11 (15.28)
Bone	10 (13.89)
Other	3 (4.11)
CEA > 10 ng/L	17/54 (31.48)
CA199 > 80 U/mL	33/55 (60.00)

Patients were evaluated at the start of every cycle. Physical examinations were performed; symptoms and toxic effects were monitored; liver and renal function was assessed; complete blood counts were measured; and electrocardiograms were performed. Tumor response was measured according to the Response Evaluation Criteria in Solid Tumor (RECIST) 1.0 criteria. Tumor response was assessed using computed tomography at 6 weeks in patients who had completed treatment. Tumor control was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

The chemotherapy dose intensities administered were as follows: oxaliplatin (85 mg/m^2/2w, 130 mg/m^2/3w); irinotecan (180 mg/m^2/2w, 100 mg/m^2, d1, d8/3w); docetacel (60 mg/m^2/3w); gemcitabine (1.0 g/m^2, d1, d8/3w) and fluorouracil (400 mg/m^2, d1, d2, 600 mg/m^2, d1, d2/2w); capecitabine (1000 mg/m^2, bid, d1–14/3w); S1 (80 mg/m^2, d1–14/3w); pemetrexed (500 mg/m^2/3w); and bevacizumab (5 mg/2w, 7.5 mg/kg/3w).

Statistical analysis

We created descriptive summaries for each demographic and clinical variable. The following variables were examined using univariate and multivariate analyses for progression-free survival (PFS) and overall survival (OS): age, sex, histologic grade, mucinous histology, primary site, stage at presentation, and initial site of metastasis.

The Chi-square test was used to assess the independence between 2 categorical variables. Survival curves were calculated from the start of chemotherapy use the Kaplan-Meier method. The log-rank test was used to evaluate the association between OS and PFS. In the multivariate analysis, a Cox proportional hazards model was used to assess the effect of ≥ 2 variables on OS and PFS. The statistical analyses were performed using SPSS software.

Results

Patient characteristics

Table 1 showed the clinical characteristics of the 73 patients who met the inclusion criteria. The median age was 54.0 years (range 31–78 years). Of the 73 patients who presented with metastatic disease, 44 patients underwent surgical resection of their primary tumor, 18 patients underwent a surgical bypass, and 11 patients underwent a biopsy. The location of the primary tumor was the duodenal bulb in 4 patients, the descending duodenum in 49 patients, the horizontal duodenum in 4 patients, the ascending duodenum in 2 patients and was not specified in 14 patients. Histologic grading was available for 61 patients. Of these, 7 patients had a well-differentiated tumor, 40 patients had a moderately differentiated tumor, and 14

patients had a poorly differentiated carcinoma. Eleven patients (15.07%) had a tumor with mucinous histologic features. Forty-one patients who initially presented with tumor stages II and III subsequently developed metastatic disease. Among patients with stage IV tumors, 52 patients (72.22%) had distant lymph node metastases, 29 patients (40.28%) had liver metastases, 14 patients (19.44%) had peritoneum metastases, and 11 patients (15.28%) had lung metastases. Tumor markers were evaluated in only 54 patients for carcinoembryonic antigen (CEA) levels and in 55 patients for carbohydrate antigen (CA199) levels. An elevated CEA level was noted in 17 patients (31.48%) and an elevated CA199 level was noted in 33 patients (60.00%).

First-line chemotherapy treatment response

Of the 10 patients who received 5-flurouracil-based therapy without a platinum agent, 4 patients received gemcitabine, 2 patients received irinotecan and bevacizumab, 1 patient received docetaxel, 1 patient received HCPT, and 2 patients received fluorouracil alone. Of the 35 patients who received 5-flurouracil-based therapy with a platinum agent, 19 patients received fluorouracil and oxaliplatin, 8 patients received capecitabine and oxaliplatin, 4 patients received S1 and oxaliplatin, and 4 patients received fluorouracil and cisplatin. Of the 5 patients who did not receive fluorouracil and a platinum agent, 2 patients received gemcitabine and oxaliplatin, 1 patient received pemetrexed and oxaliplatin, 1 patient received gemcitabine and cisplatin, and 1 patient received paclitaxel and cisplatin. Of the 2 patients who did not receive fluorouracil and platinum, 1 patient received irinotecan and bevacizumab, and 1 patient received docetaxel and irinotecan (Table 2).

The overall response rate (RR) of the 52 patients who received chemotherapy was 21.15%. Eleven patients had partial responses, 25 had stable disease, and 16 had disease progression. The disease control rate (DCR) of these 52 patients was 69.23%. The patients who received fluorouracil and oxaliplatin exhibited better RR compared with patients who received other chemotherapy combinations (31.57% vs. 14.70%, $\chi^2 = 1.5248$, $P = 0.2169$). The patients who received fluorouracil and platinum exhibited better RR compared with patients who received other chemotherapy combinations (25.71% vs. 11.76%, $P = 0.1590$). One patient with right atrium metastasis who received FOLFOX was alive 44 months after a Whipple operation.

Survival after first-line chemotherapy treatment

Of the 73 patients included in this study, the median follow-up was 49 months and the median OS was 11.47 months. Patients who received palliative chemotherapy had a higher median OS than patients who did not receive chemotherapy (14.28 vs. 5.20 months, HR = 0.205, 95% CI: 0.077 to 0.547, $P = 0.0016$). Compared with other chemotherapy regimens, patients treated with fluorouracil and oxaliplatin had a better PFS (5.85 vs. 4.21 months, HR = 0.627, 95% CI: 0.186 to 2.424, $P = 0.5440$) and OS (15.666 vs. 11.320 months, HR = 1.070, 95% CI: 0.446–2.568, $P = 0.8798$) (Table 3 and Fig. 1).

Based on the multivariate analysis, mucinous histology (7.70 vs. 12.85 months, HR = 3.206, 95% CI: 1.197 to 8.587, $P = 0.0205$) and liver metastasis (10.00 vs. 14.13 months, HR = 2.77, 95% CI: 1.268 to 6.047, $P = 0.0106$) were independent factors associated with poor outcome. There were no statistically significant differences in OS for the factors of age, sex, histologic grade, primary site, stage at presentation, or initial site of metastasis ($P > 0.05$).

Second- and third-line chemotherapy

Twenty-two patients received second-line or third-line chemotherapy. Most patients who received first-line platinum-based chemotherapy subsequently received iri-

Table 2 First-line chemotherapy regimens for metastatic duodenal carcinoma [*n* (%)]

Chemotherapy	Cases	Response
Fluorouracil and no platinum	10	1 (10.00)
Fluorouracil and gemcitabine	4	1
Fluorouracil, irinotecan and bevacizumab	2	0
Fluorouracil and docetaxel	1	0
Fluorouracil and HCPT	1	0
Fluorouracil alone	2	0
Fluorouracil and platinum	35	9 (25.71)
Fluorouracil and oxaliplatin*	19	6 (31.58)
Capecitabine and oxaliplatin	8	2
S1 and oxaliplatin**	4	1
Fluorouracil and cisplatin***	4	0
No fluorouracil and platinum	5	1 (20.00)
Gemcitabineand oxaliplatin	2	0
Pemetrexed and oxaliplatin	1	0
Gemcitabine and cisplatin	1	0
Paclitaxel and cisplatin	1	1
No fluorouracil and no platinum	2	0
Irinotecan and Bevacizumab	1	0
Docetacel and Irinotecan	1	0

* Fluorouracil, oxaliplatin, and docetaxel (1 patient). Fluorouracil, oxaliplatin, and bevacizumab (1 patient); ** S1, oxaliplatin, and docetaxel (1 patient); *** Fluorouracil, cisplatin, and paclitaxel (1 patient)

Table 3 Cox proportional hazard results for survival

Outcome	*P* value	HR	95% CI
Chemotherapy	0.0016	0.205	0.077–0.547
Liver metastasis	0.0106	2.770	1.268–6.047
Mucinous histology	0.0205	3.206	1.197–8.587

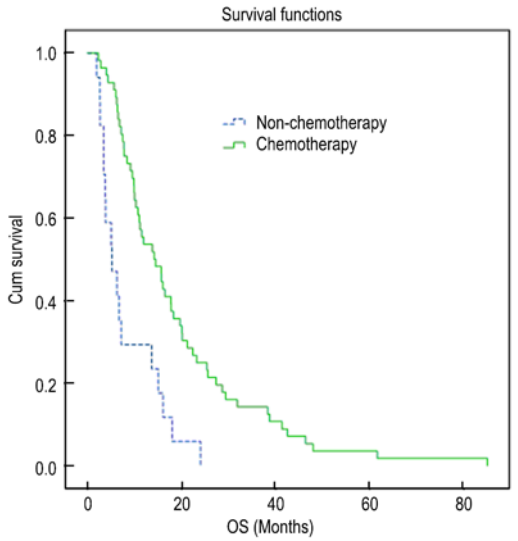

Fig. 1 Kaplan-Meier survival analysis of overall survival (OS)

notecan-based therapy. One patient who received irinotecan and capecitabine responded to treatment.

Discussion

Primary duodenal carcinoma is the most common small bowel cancer [5]. Because of the rarity of PDC, no prospective randomized controlled study has evaluated the role of chemotherapy in the treatment of advanced or metastatic PDC and there is no established standard chemotherapy for this disease. Numerous studies have determined the role of chemotherapy in the treatment of advanced or metastatic small bowel adenocarcinoma (including PDC). Overman *et al* reported that chemotherapy with 5-fluorouracil and a platinum compound improved outcome in metastatic small bowel adenocarcinoma patients (including 30 cases of PDC) [9]. In the current study, we observed that patients with advanced PDC who received palliative chemotherapy had a longer OS compared with patients who did not receive chemotherapy (14.28 vs. 5.20 months, HR = 0.205, 95% CI: 0.077 to 0.547, $P = 0.0016$). Another retrospective study by Koo *et al* conducted at the Asan Medical Center, Seoul, Korea, reported palliative chemotherapy may improve survival outcomes (11.8 vs. 5.7 months) in patients with advanced SBA (including 71 caces of PDC) [10], similar to our findings.

Patients with advanced PDC are often treated using the same chemotherapy regimens as patients with advanced gastric or colorectal cancers. The overall response and disease control rates of the 52 patients who received chemotherapy were 21.15% and 69.23%, respectively. Approximately 70% of the patients benefited from chemotherapy. Thirty-five patients (66.04%) received platinum combined with 5-flurouracil. The patients who received fluorouracil and oxaliplatin (FOLFOX) exhibited better RR (31.57% vs. 14.70%) and OS (15.67 vs. 11.32months) compared with patients who received other chemotherapy combinations, but there were no statistically significant differences ($P = 0.2169$ and 0.879, respectively). The overall RR among FOLFOX-treated patients with advanced PDC (31.57%) was similar to those in prior reports (30%–34.2%) [11–13]. It would be worthwhile to confirm these findings in a larger study.

Using multivariate analysis, mucinous histology and liver metastasis were independent factors predictive of poor prognosis in patients with advanced PDC. We found that compared with patients without liver metastasis, patients with liver metastasis had a poorer OS (10.00 months vs. 14.13 months, HR = 2.77, 95% CI: 1.268 to 6.047, $P = 0.0106$), similar to prior reports [9]. It has been shown that patients with liver metastasis have poor survival outcomes.

It is generally recognized that colorectal cancer with mucinous histology has a worse prognosis than non-mucinous tumors. In some studies, mucinous histology has been shown to be a negative prognostic factor, with a high frequency of metastasis [14–15], less responsiveness to chemotherapy, and poor OS [16]. We found 11 patients with a histologically-confirmed diagnosis of mucinous PDC. The median OS for mucinous PDC patients was 7.70 months compared with 12.85 months for patients in the non-mucinous group ($P = 0.01$), which may correlate with a high metastasis frequency [14–15] and a poorer response to chemotherapy. There is little information in the literature on the use of second-line and third-line chemotherapy agents for PDC. Overman *et al* observed responses to second- and third-line chemotherapy in 6 of 57 patients [9]. Zaana *et al* observed that the overall response was 20% using a FOLFIRI second-line therapy agent after a first-line FOLFOX regimen [17]. In our study, 22 patients received either second-line or third-line therapy, and only 1 patient responded to irinotecan and capecitabine therapy.

Our results should be interpreted with caution because this study had several limitations including a retrospective design and the selection of patients from 3 institutions, which may have introduced selection biases.

Conclusions

Palliative chemotherapy may improve the OS of patients with advanced PDC. FOLFOX seemed to be more effective in advanced PDC. Mucinous histology and liver metastasis were the main prognostic factors in patients with advanced PDC.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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