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Duodenal stenting followed by systemic chemotherapy for patients with pancreatic cancer and gastric outlet obstruction

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ABSTRACT

Objectives: Endoscopic duodenal stenting has recently been proposed as a substitute for surgical gastrojejunostomy for the treatment of gastric outlet obstruction. We aimed to evaluate the efficacy and safety of duodenal stenting followed by systemic chemotherapy for patients with advanced pancreatic cancer with gastric outlet obstruction.

Methods: This was a single-center, retrospective cohort study, conducted at an academic medical center, of 71 patients with advanced pancreatic cancer and gastric outlet obstruction (mean age: 67.6 years; range: 31–92 years) who underwent duodenal stenting with or without subsequent chemotherapy. Overall survival, duration of oral intake of foods, the rate of introduction of chemotherapy, progression-free survival, and adverse events were evaluated.

Results: Stent placement was technically successful in 69 (97%) patients. Thirty-six (51%) patients were treated with chemotherapy: 17 with gemcitabine alone, 15 with S-1 alone, 3 with FOLFIRINOX, and 1 with paclitaxel. Median progression-free survival and overall survival after chemotherapy were 2.6 months (95% confidence interval: 1.3–3.9 months) and 4.7 months (95% confidence interval: 2.6–6.8 months), respectively. Cases of grade 3 anemia were frequently observed during chemotherapies following duodenal stenting (32%). Tumor stage, performance status, neutrophil-to-lymphocyte ratio, and introduction of chemotherapy were independent prognostic factors for survival (hazard ratios of 3.73, 2.21, 2.69, and 1.85 with p-values of <0.001, 0.010, <0.001, and 0.045, respectively).

Conclusions: The findings of this study suggest that endoscopic duodenal stenting is an advantageous treatment in advanced pancreatic cancer patients with gastric outlet obstruction regarding its safety and smooth conduction of subsequent chemotherapies.

1. Introduction

Pancreatic adenocarcinoma is the fourth leading cause of death in the United States, where it was responsible for approximately 40,000 deaths in 2014 [1], and it was the fifth leading cause of death in Japan in 2012 [2]. Although surgical resection is the only curative treatment for this disease, more than 80% of cases of pancreatic adenocarcinoma are diagnosed in an unresectable stage [3]. Patients whose adenocarcinoma is at an unresectable stage or those who experience recurrent disease following surgery are recommended to undergo systemic chemotherapy [4]. Recent advances in chemotherapy have led to improved survival in such cases [5–8]; however, chemotherapy is usually insufficient for long-term survival.

Tumor invasion into the stomach, duodenum, or proximal jejunum can cause gastric outlet obstruction (GOO), which is a life-threating comorbidity in patients with advanced pancreatic cancer. GOO occurs in approximately 10–20% of cases of pancreatobiliary cancer [9–11]. Surgical gastrojejunostomy has been widely used as a palliative treatment for GOO, and it leads to improvements in oral

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intake of food [12]. Endoscopic duodenal stenting, which was first reported in the early 1990s [13], is a non-invasive treatment option for patients with advanced cancers with GOO. The efficacy of gastrojejunostomy versus endoscopic stenting has been evaluated in previous studies, including two reviews [14,15]. These systematic reviews revealed no differences in the incidence of adverse events and overall survival between gastrojejunostomy and endoscopic stenting; however, endoscopic stenting has several advantages, such as a shorter hospital stay, and it is less invasive than gastrojejunostomy [15]. Furthermore, several studies have reported that patients undergoing endoscopic stenting had an acceptable survival time of longer than three months [15,16].

We speculated that endoscopic stenting might be a more favorable option than gastrojejunostomy prior to the introduction of chemotherapy. In addition, endoscopic stenting might provide survival benefits to patients with advanced pancreatic cancer. The treatment strategy of endoscopic stenting followed by systemic chemotherapies is supported by a report that suggested that subsequent chemotherapies would prolong the duration of stent patency and vice versa [17]. In the current study, we evaluated endoscopic stenting followed by systemic chemotherapy for patients with GOO and advanced pancreatic cancer; this is the first report to evaluate the efficacy and safety of this combined treatment.

2. Methods

2.1. Patients

We enrolled 71 consecutive patients with advanced pancreatic cancer who suffered from GOO between April 2010 and February 2014 and were treated at our institution. Candidates for endoscopic duodenal stenting met the following criteria: 1) unresectable or recurrent disease that could not be cured by surgical resection, 2) histologically or cytologically proven pancreatic cancer, and 3) GOO caused by a stricture located between the stomach and the horizontal portion of the duodenum that was confirmed by radiological or endoscopic findings. Duodenal stent placement was contraindicated for patients who met the following conditions: 1) presence of strictures in sites other than the gastroduodenum or a functional disorder caused by peritoneal dissemination, 2) hemorrhagic status, 3) plans to undergo irradiation to the lesion in the future. All patients provided written informed consents for duodenal stent placement, and all of the applicable patients to subsequent chemotherapy also provided written informed consents. In addition, this retrospective cohort study was approved by the Institutional Review Board of Kanagawa Cancer Center in October, 2015.

2.2. Duodenal stenting

We used two types of uncovered stents. From April 2010 to December 2013, we used WallFlex duodenal stents (Boston Scientific Corporation, Marlborough, MA, USA) of 60 mm, 90 mm, or 120 mm in length and 22 mm in diameter, with a proximal flare of 24 mm in diameter. From January 2014 to April 2015, we used either WallFlex duodenal or Niti-S D pyloric/duodenal stents (Taewoong Medical Co., Ltd., Seoul, Korea) of 60 mm, 80 mm, 100 mm, or 120 mm in length and 22 mm in diameter without proximal flares. Stent placement was performed under sedation and the stricture was identified mainly endoscopically. In cases in which the stricture was located at a distal part of the horizontal portion of the duodenum, we performed fluoroscopic duodenography with contrast media (Gastrografin Oral Enema, Bayer HealthCare, Leverkusen, Germany) to identify the stricture. A 0.089-inch guidewire (Hydra Jagwire, Boston Scientific Corporation) was inserted through the stricture, and the duodenal stent was positioned across the stricture under fluoroscopic guidance. The stent size was chosen according to the length of the stricture, and the oral side of the stent was positioned proximal to the pyloric ring when its axial force might cause perforation and ulcers in the duodenal mucosa. In addition, we tried not to place the duodenal stent across the ampulla in patients who had strictures apart from the ampulla in order to prevent it from causing obstructive jaundice or acute pancreatitis. Finally, the stent was deployed and its patency was confirmed by the injection of contrast media. After placement of the stent, patients were allowed to resume consumption of liquids on day one, soft foods on day two, and solid foods on day three as long as no symptoms of GOO exacerbation were observed. In cases of GOO recurrence, a secondary duodenal stent was placed using the stent-in-stent technique.

2.3. Systemic chemotherapy following duodenal stenting

Patients who met the eligibility criteria underwent systemic chemotherapy following duodenal stenting. The eligibility criteria for chemotherapy were as follows: 1) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; 2) possibility of oral intake; 3) adequate hepatic and renal function; 4) preserved bone marrow function: neutrophil count > 1500 μL/mm^3 (3500–9800 μL/mm^3); platelet count > 100,000 μL/mm^3 (13,000–369,000 μL/mm^3); and 5) a life expectancy of at least three months. We selected the chemotherapy regimens according to each patient's condition and/or consent. Possible regimens included gemcitabine (Gemzar, Eli Lilly and Company, Indianapolis, IN, USA), S-1 (TS-1, Taiho Pharmaceutical Co., Ltd., Tokyo, Japan), FOLFIRINOX (fluorouracil [5-FU injection, Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan]; leucovorin [Isovorin injection, Pfizer Inc., New York, NY, USA]; irinotecan [Topotecin, Daiichi-Sankyo Co., Ltd., Tokyo, Japan]; oxaliplatin [Elplat, Yakult Honsha Co., Ltd., Tokyo, Japan]), and paclitaxel (Taxol, Bristol-Myers Squibb, New York, NY, USA). Patients did not receive irradiation because it can result in perforation of the duodenal wall [18]. Chemotherapy was continued until disease progression, intolerable adverse events, or patient's refusal.

2.4. Clinical outcomes

The technical success of stent placement was defined as the achievement of stent deployment across the stricture. Clinical success was defined as any improvement in the symptoms, according to the GOO scoring system [10]: score 0, no oral intake; score 1, liquids only; score 2, soft foods; score 3, solid foods/full diet. The duration of oral intake was measured from the date of restarting oral intake to the last date of oral intake due to any cause or the last date of follow-up. Overall survival was measured from the date of stent placement to the date of death due to any cause or the last follow-up. Progression-free survival was measured from the date of initiation of the systemic chemotherapy after stent placement to the date of discontinuation or the last follow-up. Adverse events were retrospectively evaluated using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) [19]. Adverse events that occurred within two weeks after stent placement were defined as early adverse events, and those that occurred later than two weeks after stent placement were defined as late adverse events. The treatment effects of chemotherapy were radiologically evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [20].

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