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Factors associated with failure to complete adjuvant chemotherapy in pancreatic cancer

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Abstract

BACKGROUND: The importance of completing adjuvant chemotherapy in pancreatic cancer is becoming recognized. However, the clinicopathological factors associated with failure to complete adjuvant chemotherapy remain unclear.

METHODS: A total of 135 patients were analyzed to identify the factors associated with failure to complete adjuvant chemotherapy.

RESULTS: Ninety patients completed planned adjuvant chemotherapy, whereas 45 patients failed to complete adjuvant chemotherapy. Lower preoperative prognostic nutritional index, intraoperative blood transfusion, and organ and/or space surgical site infection, and advanced tumor stage were associated with failure to complete adjuvant chemotherapy. Neoadjuvant chemoradiotherapy was associated with significantly lower prognostic nutritional index, less incidence of organ and/or space surgical site infection, and earlier tumor stage, suggesting the conflicting effects of neoadjuvant chemoradiotherapy on completing adjuvant chemotherapy.

CONCLUSIONS: Several clinicopathological factors including patient conditions and perioperative events were associated with failure to complete adjuvant chemotherapy.

Despite recent improvements in diagnostic and therapeutic modalities, pancreatic cancer still has an extremely poor prognosis.[1] Although only surgery may lead to a complete cure, most patients develop recurrence even after curative-intent surgery.[2–4] Since randomized controlled clinical trials have demonstrated a significant efficacy of gemcitabine (GEM) as postoperative adjuvant treatment,[5,6] surgeons and oncologists have come to use adjuvant chemotherapy more actively than before. At present,

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adjuvant chemotherapy is one of the mainstays for the treatment of resectable pancreatic cancer.

Pancreatic resection is generally recognized as highly invasive surgery, although it has come to be relatively safely performed especially at high-volume surgical centers.[7–10] Even in well-experienced institutions, the postoperative complications, such as pancreatic fistula, postoperative hemorrhage, and surgical infections, often develop and can occasionally lead to fatal conditions. In addition, late surgical complications including alimentary dysfunction, pancreatic endocrine, and exocrine insufficiency, may also develop.[10–14] As a result, the full recovery from surgery may be delayed and the poor condition may last for a long time in some patients. Importantly, such unfavorable state may reduce the tolerability of adjuvant chemotherapy. In fact, only 62% of patients in the CONKO-001 trial received the planned full dose of adjuvant GEM.[5] A recent large-scale clinical study has shown that the completion of planned adjuvant chemotherapy rather than early initiation was a critical prognostic factor for patients with resectable pancreatic cancer.[15] Although the importance of the completion of adjuvant chemotherapy has been gradually recognized, there are few studies to address the underlying mechanisms of failure to complete adjuvant chemotherapy in resectable pancreatic cancer patients.

We hypothesized that to reveal the causes for failure to complete adjuvant chemotherapy might lead to develop new therapeutic strategy and to improve the patient survival. Therefore, the aim of this study was to investigate the clinicopathological factors associated with failure to complete adjuvant chemotherapy in patients after curative-intent surgery for pancreatic cancer.

Methods

A total of 168 patients who underwent pancreatectomy for invasive adenocarcinoma of the pancreas between May 2004 and December 2011 at Nara Medical University Hospital were evaluated. Twenty-two patients who had positive peritoneal cytology at laparotomy, macroscopic incomplete resection, or distant metastasis were excluded. Furthermore, 11 patients who did not receive any adjuvant chemotherapy were also excluded. The remaining 135 patients were enrolled in this study. Patients provided written informed consent before treatment according to the rules and regulations of our institution.

Preoperative therapy was not performed in patients between 2004 and July 2008. Since September 2008, all patients were subjected to neoadjuvant chemoradiotherapy (NACRT) to achieve local control and possibly complete cure, as previously reported.[16] As postoperative adjuvant therapy, some patients received combination therapy comprising a weekly hepatic arterial chemotherapy infusion of weekly high-dose 5-fluorouracil (WHF) combined with systemic infusion of GEM as previously described.[17] Other patients received adjuvant chemotherapy with GEM or S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) alone based on the patient's condition or choice. The scheduled regimen of systemic GEM was 6 cycles. Each cycle consisted of weekly 30-minute intravenous infusions of GEM 1,000 mg/m^2 for 3 weeks, followed by a 1-week rest period. S-1 was administered orally twice a day at a dose of 80 mg/m^2/day from days 1 to 28, followed by a 2-week rest period. Three initial doses were established according to the body surface area (BSA) as follows: BSA less than 1.25 m^2, 80 mg/day; 1.25 m^2 less than or equal to BSA less than 1.50 m^2, 100 mg/day and 1.50 m^2 less than or equal to BSA, 120 mg/day.

The completion of adjuvant therapy was defined, regardless of dosing period, when it reached the planned number or cycles of chemotherapy: WHF/GEM, 9 times infusion of WHF and 18 times administrations of GEM; GEM, 18 times administrations of GEM; S-1, 16 weeks of oral administration. Preoperative body mass index was calculated as weight (kg)/height^2 (m^2). As a barometer of nutritional assessment, Onodera's prognostic nutritional index (PNI) was used.[18] The preoperative PNI was calculated as 10 $\times$ albumin (g/dL) + .005 $\times$ total lymphocyte count (per mm^3). Pancreatic fistula and delayed gastric emptying were defined according to the guidelines of the International Study Group on Pancreatic Fistula and International Study Group of Pancreatic Surgery, respectively.[19,20] Organ/space surgical site infection (SSI) within 30 days postoperatively was defined according to the guidelines of the Centers for Disease Control and Prevention.[21] Stage classification and the evaluation of resected specimens were performed according to the seventh edition of the American Joint Committee on Cancer/Union for International Cancer Control (UICC) tumor, node, metastasis classification.[22]

Statistical analysis

The clinicopathological parameters were compared using the Student's *t* test, the chi-square test, or Fisher's exact test as appropriate. Continuous variables were expressed as mean values $\pm$ standard deviation. Using receiver operating characteristic curve analysis, we defined the cutoff values of the preoperative PNI and operative time for detecting patients who did not complete the adjuvant chemotherapy. A Cox proportional hazards model was used for univariate analysis of patient survival. A multiple logistic regression analysis was used to identify the factors independently associated with failure to complete adjuvant chemotherapy. Statistical analyses were performed using JMP statistical discovery software (JMP version 11.0; SAS Institute, Cary, NC). A P value less than .05 was considered statistically significant.

Results

A total of 135 patients who had undergone pancreatic resection were included for the final analysis. Patient