Abstract. The aim of the present study was to investigate the early treatment outcomes of combined gemcitabine and nab-paclitaxel treatment for locally advanced unresectable pancreatic cancer (LURPC). The subjects comprised 7 patients with LURPC receiving the abovementioned combination therapy at the Hirosaki University Hospital (Hirosaki, Japan) between January and September, 2015. The clinicopathological factors, adverse events and response to treatment were investigated. To determine whether the cases were unresectable, the National Comprehensive Cancer Network guidelines, version 2. 2015, were applied. The patients underwent a median of 4 (range, 2-7) courses of treatment. The response to treatment was evaluated using the Response Evaluation Criteria In Solid Tumors. The subjects included 1 male and 6 female LURPC patients, with a median age of 71 years (range, 59-78 years). The tumor was located in the head and body of the pancreas in 6 and 1 patients, respectively. No patients achieved a complete response, 5 achieved a partial response, 2 had stable disease, and none exhibited progressive disease. The response rate was 71%. The mean tumor diameter decreased significantly from 35 mm (range, 24-60 mm) prior to treatment to 22 mm (range, 20-35 mm) following treatment. Two patients were downstaged. The mean carbohydrate antigen (CA) 19-9 values decreased significantly from 767 U/ml (range, 14-1,977 U/ml) prior to treatment to 35 U/ml (range, 14-123 U/ml) following treatment. Adverse events classified as grade ≥3 occurred in 4 patients (57%): 3 patients (43%) suffered from neutropenia and 1 patient (14%) developed bilateral cellulitis of the lower extremities. No patients experienced an increase in disease severity, and all were able to continue treatment following temporary withdrawal or dosage reduction. Therefore, combined treatment with gemcitabine and nab-paclitaxel had favorable tumor-reducing effects and was not associated with severe adverse events, suggesting that this is a useful therapeutic strategy for patients with LURPC.

Introduction

Pancreatic cancer (PC) has an extremely high degree of malignancy, and the number of affected patients is increasing annually (1). Currently, PC is the fourth highest cause of cancer-related mortality among US adults and the fifth and fourth leading cause of death among Japanese men and women, respectively (1,2). Resection is the only form of treatment associated with a complete cure, but only 10-20% of cases are resectable and the majority of the cases involve metastatic or locally advanced unresectable PC (LURPC) (3). LURPC accounts for 30-35% of all PC cases (4), and its treatment options include chemotheray or chemoradiotherapy (CRT). However, its prognosis remains poor, and there is an urgent need for novel treatment methods (5).

The recently conducted MPACT trial verified that a combination therapy comprising gemcitabine (GEM) and nab-paclitaxel (nab-PTX) significantly prolonged the survival of patients with metastatic PC compared with a therapy comprising GEM alone (6). The results of that study indicated that this regimen may become a new therapeutic option. However, the responses to this form of treatment for LURPC have not yet been fully elucidated. The aim of the present study was to investigate the safety and efficacy of the combination of GEM and nab-PTX for the treatment of patients with LURPC.

Patients and methods

Patients. A total of 7 patients with LURPC were treated with a combination regimen comprising GEM and nab-PTX at the Department of Gastroenterological Surgery of the Hirosaki University Hospital (Hirosaki, Japan) between January and September, 2015. The chemotherapy regimen included the administration of GEM (1,000 mg/m² on days 1, 8 and 15, every 4 weeks) and nab-PTX (125 mg/m² on days 1, 8 and 15, every 4 weeks). Resectability was determined according to the National Comprehensive Cancer Network (NCCN) guidelines, version 2. 2015 (7). The number of chemotherapy courses,
rate of change in tumor diameter, rate of change of serum carbohydrate CA19-9 values, incidence of grade ≥3 adverse events, therapeutic effects and survival time were investigated in all the cases. In an effort to determine specific response to treatment, the Response Evaluation Criteria In Solid Tumors guidelines, version 1.1 (8) were used for analyzing patient computed tomography images. Survival time was defined as the period from the date of treatment initiation to the date on which the outcome was achieved. Overall patient survival was analyzed using the Kaplan-Meier method. All analyses were performed using the IBM SPSS® Statistics version 24.0 for Windows (IBM, Armonk, NY, USA). This study was approved by the Human Research Ethics Committee of Hirosaki University (no. 2016-1038) and informed consent was provided by all the participants.

Results

Patient characteristics. The patient characteristics are summarized in Table I. The median patient age was 71 years (range, 59-78 years), and the subjects comprised 1 male and 6 female LURPC patients. The tumor was located at the body of the pancreas in 1 and in the head of the pancreas in 6 subjects. The criteria for diagnosing a case as unresectable were as follows: Solid tumor in contact with the celiac axis >180˚ in 3 subjects, solid tumor in contact with the common hepatic artery with extension to the hepatic artery bifurcation in 2 subjects, an unreconstructible portal vein due to tumor involvement in 1 subject, and an unreconstructible portal vein/superior mesenteric vein involvement in 1 subject. The patients underwent a median of 4 (range, 2-7) courses of chemotherapy. No patients achieved a complete response, 5 achieved a partial response, 2 had stable disease, and none had progressive disease. The response rate was 71% (Fig. 1).

Therapeutic effects. The therapeutic effects of the combination treatment are summarized in Table II. The median tumor diameter significantly decreased from 35 mm (range, 24-60 mm) prior to treatment to 22 mm (range, 20-35 mm) following treatment (P=0.008); the median rate of tumor shrinkage was 37% (range, 0-57%). The mean serum CA19-9 values significantly decreased from 35 mm (range, 24-60 mm) prior to treatment to 22 mm (range, 20-35 mm) following treatment (P=0.038); the median rate of tumor shrinkage was 37% (range, 0-57%). The median tumor regression rate was 37% (range, 0-57%), and powerful tumor-reducing effects were achieved. Furthermore, the median survival time was 13.3 months, which is considered to be a favorable outcome.

The NCCN guidelines recommend chemotherapy or CRT for the treatment of LURPC when the performance status of the patients is favorable. To date, chemotherapy using GEM, 5-fluorouracil (5-FU)/leucovorin (LV) or capecitabine, or combined treatment comprising radiation in the form of CRT, are recommended. In recent years, 5-FU/LV plus oxaliplatin and irinotecan (FOLFIRINOX regimen) have been reported to be useful and recommended as a new treatment regimen. Recent reports regarding the treatment of LURPC are presented in Table III. Habermehl et al investigated CRT using GEM for the treatment of LURPC and reported a response rate (RR) of 9%, with a median survival time of 12.3 months (15). In addition, Faris et al evaluated the FOLFIRINOX regimen for the treatment of LURPC and found an RR of 27%, as well as favorable treatment outcomes (median disease-free survival: 11.3 months); however, the median survival time was not reported (3). Moreover, Nanda and Blazer et al also reported favorable outcomes when they compared FOLFIRINOX with CRT for the treatment of LURPC, with median survival times of 18.6 and 12.2 months, respectively (16,17). During the present study, the RR was 71%, and although the median survival time was not calculated, the mean survival time was 13.3 months. These findings suggest that the combination therapy comprising GEM and nab-PTX is effective for treating patients with LURPC.

There are reports of severe adverse events during chemotherapy and CRT treatment for LURPC. Chen et al performed a meta-analysis comparing CRT, chemotherapy alone and
radiotherapy alone for LURPC, and reported that grade ≥3 adverse events were common (18). In addition, a phase III trial (FFCD-SFRO trial) compared CRT using 5-FU and cisplatin to chemotherapy using GEM alone. They found that, compared with the chemotherapy group, the CRT group was associated with a significantly higher incidence of hematotoxic and non-hematotoxic adverse events, such as infection, vomiting and diarrhea (66 vs. 40%, respectively; P=0.008) (19). The same trial also observed a significant prolongation of median survival time in the chemotherapy group (13.0 vs. 8.6 months; P=0.03), suggesting that chemotherapy is useful for treating LURPC (19).

Moreover, another phase III trial (ECOG-4201 trial) compared CRT using GEM alone to chemotherapy using GEM alone. There were no significant differences in the incidence of grade ≥3 adverse events (79 vs. 77%, respectively; P=0.1) and the median survival time was reported to be significantly longer in the CRT group (11.1 vs. 9.2 months, respectively; P=0.017) (20). There continues to be a multitude of such contradictory reports and discussion regarding the usefulness of CRT for the treatment of LURPC (21).

Table I. Characteristics of patients with locally advanced unresectable pancreatic cancer.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, years</th>
<th>Gender</th>
<th>Location</th>
<th>Factor determining unresectability</th>
<th>Number of chemotherapy cycles</th>
<th>RECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>F</td>
<td>Head</td>
<td>Solid tumor contact with CA &gt;180˚</td>
<td>7</td>
<td>PR</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>F</td>
<td>Head</td>
<td>Unreconstructible PV due to tumor involvement</td>
<td>5</td>
<td>SD</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>Head</td>
<td>Solid tumor contact with CHA with extension to hepatic artery bifurcation</td>
<td>2</td>
<td>PR</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>F</td>
<td>Head</td>
<td>Solid tumor contact with CA &gt;180˚</td>
<td>4</td>
<td>PR</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>F</td>
<td>Body</td>
<td>Solid tumor contact with CA &gt;180˚</td>
<td>2</td>
<td>SD</td>
</tr>
<tr>
<td>6</td>
<td>78</td>
<td>F</td>
<td>Head</td>
<td>Unreconstructible PV/SMV due to tumor involvement</td>
<td>4</td>
<td>PR</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>F</td>
<td>Head</td>
<td>Solid tumor contact with CHA with extension to the hepatic artery bifurcation</td>
<td>2</td>
<td>PR</td>
</tr>
</tbody>
</table>

F, female; M, male; CS, conversion surgery; CA, celiac axis; CHA, common hepatic artery; PV, portal vein; SMV, superior mesenteric vein; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria In Solid Tumors.

Table II. Evaluation of the chemotherapy for locally advanced unresectable pancreatic cancer.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
</table>
| Tumor diameter, mm [median (range)] | Pre CTx 35 (24-60)  
Post CTx 20 (15-35)  
Reduction rate (%) 37 (0-57)  
CA19-9, U/ml Pre CTx 247 (14-1,977)  
Post CTx 35 (4-123)  
Reduction rate (%) 92 (47-98)  
RR, % 71 (CR, 0; PR, 5; SD, 2; PD, 0)  
Grade ≥3 adverse events, n (%)  
Neutropenia 3 (43)  
Cellulitis 1 (14)  
CS 2 (29)  
R0 resection, n/total (%) 2/2 (100)  |

RR, response rate; CS, conversion surgery; CTx, chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Figure 1. Waterfall plot of maximum percentage changes from baseline in the size of target lesions according to the Response Evaluation Criteria In Solid Tumors (n=7). A total of 5 patients exhibited partial response (71%) and 2 patients had stable disease (29%).
In Table III, when Habermehl et al investigated CRT as a treatment for LURPC, CS was performed in 26% of the cases and the rate of clear surgical margins was 39% (15). When Faris et al studied the FOLFIRINOX regimen for treating LURPC, they reported that CS was performed in 22% of the cases and the rate of clear surgical margins was 60%, indicating more favorable treatment outcomes compared with those observed using CRT (3). In the present study, CS was performed in 29% of the cases and the rate of clear surgical margins was 100%. Thus, combination therapy comprising GEM and nab-PTX is a potential treatment option associated with a higher CS rate, a higher rate of clear surgical margins, and a longer survival time compared with those observed with CRT or FOLFIRINOX.

Based on the abovementioned findings, this combination therapy is associated with a low incidence of adverse events, maintains the quality of life and markedly prolongs survival for patients with LURPC; thus, we consider it to be a useful form of treatment for such cases. CS is common during LURPC and should be considered as an important and novel treatment strategy. However, the present study was associated with the following limitations: i) The patient sample was very small, ii) the study design was retrospective and iii) the period of observation was brief. Thus, the usefulness of the combination therapy comprising GEM and nab-PTX for patients with LURPC requires verification by future prospective studies.

Acknowledgements

The authors would like to thank Crimson Interactive Pvt. Ltd. (Ulatus)-www.ulatus.jp for their assistance with the manuscript translation and editing.

References


