TREATMENT OF NON-RESECTABLE PancreATIC CANCER WITH
5-FLUOROURACIL, LEUCOVORIN AND MITOMYCIN-C: ONE CASE
SHOWED COMPLETE REMISSION FOR 36 MONTHS

Naohiro Sata, Masaru Koizumi, Munetoshi Tsukahara, Koji Yoshizawa, Katsumi Kurihara,
and Hideo Nagai

Department of Surgery, Jichi Medical School

Key Words: Chemotherapy, complete remission, 5-fluorouracil, leucovorin, mitomycin-C,
pancreatic cancer.

Abstract
Pancreatic cancer has a dismal prognosis because most lesions are unresectable
whereas adjuvant and palliative chemotherapy exhibits poor results.

Six patients with locally unresectable pancreatic cancer were treated with
mitomycin-C (MMC) 8mg/m² on day 1 and 5-FU 375mg/m² and LV 20mg/m² on days 1 to
5. Treatment cycles were repeated every four weeks if the patient’s general condition
permitted. All patients had measurable, histologically proven adenocarcinoma and had not
undergone prior chemotherapy.

Three patients underwent hepaticojejunostomy whilst choledochal stents were
endoscopically inserted in two patients. No significant side effects of grade 3 or 4 were
observed. Five of six patients who received an average of 5 treatment cycles died of their
disease with a medial survival of 8.9 months. The remaining patient received 12 treatment cycles and 8 additional treatments without mitomycin-C and exhibited a complete remission for 36 months.

Our data suggest that MMC plus 5-FU and leucovorin is a tolerable regimen and has promising effects. Further prospective studies are needed.

Introduction

Adenocarcinoma of the pancreas is a leading cause of cancer death worldwide and is increasing in prevalence in Japan (O'Connell, 1985; Gudjonsson, 1987; Micheli, Yancik, Krogh et al., 2002). At the time of diagnosis, 80-90% of patients with pancreatic cancer have an advanced disease and less than one-fourth of tumors may be surgically removed (Martin, Weinerman, 1992; Link, Gansauge, Goerich et al., 1997; Tsuchiya, Tajima et al., 2001). Systemic chemotherapy is an alternative treatment for patients with advanced and unresectable pancreatic cancer and many clinical trials have been performed in an attempt to find the optimal anti-cancer drug regimen. The combination of 5-FU and leucovorin has been shown to have some anti-cancer effect in patients with advanced gastrointestinal and pancreatic cancer (Oman, Blind, Naredi et al., 2001; Huguier, Barrier, Valinas et al., 2001; Eckel, Lersch, Lippl et al., 2000; Figer, Sadikov, Mishaeli et al., 2000; Oettle, Arning, Pelzer et al., 2000; Burch, Block, Schroeder et al., 2000; Andre, Balosso, Louvet et al., 2000; Kornek, Schratte-Sehn, Markzell et al., 2000). However, the results for pancreatic cancer were far from satisfactory with a maximal response rate of 20-30% with either mono- or combination therapy. This pilot study was designed to examine the effect of the combination drug regime of 5-FU, leucovorin and MMC.

Patients and Methods

Patients admitted to the Jichi Medical School Hospital, Tochigi, Japan with biopsy-proven adenocarcinoma of the pancreas between June and November 2000 were
considered for inclusion in the study. Further eligibility criteria are summarized in Table I. In brief, criteria included patients with measurable disease, a life expectancy of at least 3 months, EOCG performance status <2, age of <80 years old, no significant central nerve system disease and no previous chemotherapy or radiotherapy. All patients were required to have normal hepatic, renal and bone marrow function. Six patients (four males and two females, mean age 60.7 years) matched the criteria and were enrolled in this study. Their profiles are summarized in Table II. All tumors were located in the head of the pancreas and had a mean diameter of 27.3 mm before treatment was commenced. Five patients were judged to have unresectable tumors because of the involvement of large arteries such as the superior mesenteric artery or the common hepatic artery, and the remaining patient had lung metastases. Three patients received palliative surgery and two patients required endoscopic stenting for biliary decompression.

**TABLE I**

Criteria for the chemotherapy

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Stage IVa, IVb (UICC criteria) unresectable pancreatic cancer</td>
</tr>
<tr>
<td>2.</td>
<td>age &gt; 18, &lt; 80 years old</td>
</tr>
<tr>
<td>3.</td>
<td>ECOG performance status &lt; 2</td>
</tr>
<tr>
<td>4.</td>
<td>no significant dysfunction in the central nerve system, heart, lung, and kidney</td>
</tr>
<tr>
<td>5.</td>
<td>WBC &gt; 4000/mm², Plt &gt; 100,000/mm², T.B. &lt; 2.0 mg/dl, Cr &lt; 2.0 mg/dl</td>
</tr>
<tr>
<td>6.</td>
<td>Informed consent</td>
</tr>
<tr>
<td>7.</td>
<td>Life expectancy &gt; 3 months</td>
</tr>
<tr>
<td>8.</td>
<td>No previous chemotherapy and radiotherapy</td>
</tr>
</tbody>
</table>

All patients were treated with mitomycin-C 8 mg/m² on day 1 and 5-FU 375mg/m² and LV 20mg/m² on days 1 to 5. Treatment cycles were repeated every four weeks if the patient’s general condition permitted. A dose of 75mg dipyridamole was
given orally during the treatment. Tumor size and responses were determined every four weeks by computerized tomography and/or the levels of tumor markers such as CEA, CA19-9, and DU-PAN-2. Patients were evaluated for drug toxicity after each cycle. Drug toxicity and clinical response were determined according to the World Health Organization (WHO) scales. The chemotherapy cycles would continue as much as possible. When obvious progressions of disease and/or endurable side effects were observed, we stopped the chemotherapy and cared the patients supportively.

Results

The effects of the chemotherapy were summarized in Table III. The total response rate was 16.7% by this protocol. Five patients out of six died of their disease with median survival of 8.9 months. They received an average of 5 treatment cycles and exhibited no tumor reduction by CT scanning. However, a mean period of stabilization of disease (SD) of 4.4 months was observed. We defined SD as tumor growth less than 25% by CT coupled with clinical stability. No major complications, classified as grade 3 or 4 according to WHO criteria, were associated with the chemotherapy. The most frequent adverse reactions were mild nausea and loss of appetite. No significant leucocytopenia or thrombocytopenia was observed.

One patient exhibited remarkable improvement of the disease. A 57-year-old woman with obstructive jaundice and a 40x40 mm low-density tumor in the head of the pancreas underwent laparotomy. Adenocarcinoma of the pancreas was proven by the intraoperative biopsy but the lesion was unresectable because of obvious invasion of the superior mesenteric artery. Hepaticojejunostomy was performed and palliative chemotherapy was initiated 4 weeks after operation. The serum concentration of CA19-9
### TABLE II
Profile of the cases

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Gender</th>
<th>Site</th>
<th>Tumor size (mm)</th>
<th>Operation</th>
<th>Clinical Stage</th>
<th>Distant Metastasis</th>
<th>LN Metastasis</th>
<th>PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>F</td>
<td>head</td>
<td>40</td>
<td>Hepaticojejunostomy</td>
<td>Iva</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>M</td>
<td>head</td>
<td>26</td>
<td>EMS</td>
<td>Ivb</td>
<td>Lung</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>M</td>
<td>head</td>
<td>25</td>
<td>Hepaticojejunostomy</td>
<td>Ivb</td>
<td>Liver</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>M</td>
<td>head</td>
<td>30</td>
<td>-</td>
<td>Iva</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>F</td>
<td>head</td>
<td>23</td>
<td>EMS</td>
<td>Iva</td>
<td>-</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>M</td>
<td>head</td>
<td>20</td>
<td>Hepaticojejunostomy</td>
<td>Iva</td>
<td>-</td>
<td>-</td>
<td>0</td>
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</table>

EMS: expandable metallic stent, PS: EOCG performance status, Clinical stages were classified by the criteria of UICC in 1997.

### TABLE III
Effects of chemotherapy

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Gender</th>
<th>Treatment Cycles</th>
<th>SD(M)</th>
<th>Glade 3,4 Side effects</th>
<th>Prognosis</th>
<th>Survival (M)</th>
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<tbody>
<tr>
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<td>24</td>
<td>&gt;36</td>
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<td>CR</td>
<td>&gt;36</td>
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<tr>
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<td>56</td>
<td>M</td>
<td>7</td>
<td>6.0</td>
<td>-</td>
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<td>8.1</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>M</td>
<td>3</td>
<td>3.0</td>
<td>-</td>
<td>dead</td>
<td>6.0</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>M</td>
<td>3</td>
<td>3.0</td>
<td>-</td>
<td>dead</td>
<td>6.3</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>F</td>
<td>5</td>
<td>6.0</td>
<td>-</td>
<td>dead</td>
<td>12.6</td>
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<tr>
<td>6</td>
<td>65</td>
<td>M</td>
<td>7</td>
<td>4.0</td>
<td>-</td>
<td>dead</td>
<td>11.4</td>
</tr>
</tbody>
</table>

SD: duration of stabilization of disease
Figure 1: CT findings before (1a, 1b, May 2000), LEFT top and bottom, and after (2a, 2b, May 2003), RIGHT top and bottom, induction of chemotherapy. The 4.4 cm low density area in the head of the pancreas (white arrows in 1a) and invasion to the superior mesenteric artery (white arrows in 1b) completely disappeared 36 months after induction of chemotherapy (2a and 2b).
and DU-PAN-2 dramatically fell just after the initiation of the treatment. The serum DU-PAN-2 level fell from 430 U/ml to undetectable levels after two cycles whilst the serum CA19-9 level fell from 230 U/ml to normal levels after four cycles. Decrease in tumor size was documented by CT scanning and estimated to be a partial response after 6 cycles whilst a complete response was observed after 12 cycles and has continued for 24 months (Figure 1). This patient received 12 cycles of the protocol drug regimen and a further 10 cycles without MMC. The complete response has continued for 36 months after the initial surgery.

Discussion

Pancreatic cancer has a dismal prognosis because most lesions are unresectable whilst adjuvant and palliative chemotherapy exhibit poor results. The median survival of patients with advanced unresectable, stage UICC III and IV, are 4.8 and 2 months, respectively (Link, Gansauge. Goerich et al., 1997; Link, Formentini, Papachristov et al., 1997; Raderer, Kornek, Hejna et al., 1997; Andre, Lotz, Azzouzi et al., 1996). Systemic treatment with single agents or combination therapy has not significantly changed this dismal prognosis. The US National Cancer Institute recommends chemotherapy with gemcitabine or 5-FU for UICC IVB or recurrent pancreatic cancer as standard treatment. Cisplatin (Huguier, Barrier, Valinas et al., 2001; Andre, Balosso, Louvet et al., 2000; Andre, Lotz, Azzouzi et al., 1996), leucovorin (Oman, Blind, Naredi et al., 2001; Huguier, Barrier, Valinas et al., 2001; Eckel, Lersch, Lippl et al., 2000; Figer, Sadikov, Mishaeli et al., 2000; Oettle, Arning, Pelzer et al., 2000; Burch, Block, Schroeder et al., 2000; Andre, Balosso, Louvet et al., 2000; Kornek, Schratte-Sehn, Marczell et al., 2000; Link, Formentini, Papachristov et al., 1997; Raderer, Kornek, Hejna et al., 1997), methotrexate
and interferons were used with 5-FU as biochemical modulators, and epirubicin (Raderer, Kornek, Hejna et al., 1997), mitomycin, cyclophosphamide (Eckel, Lersch, Lippl et al., 2000) and many other agents were used in an attempt to gain synergistic effects. Leucovorin is one of the most potent biochemical modulators for 5-FU and improved the survival rate of patients with colorectal cancer. Recent treatment with 5-FU and leucovorin with or without other agents such as radiation, gemcitabine (Marantz, Jovtis, Almira et al., 2001; Reni, Passoni, Panucci et al., 2001; Klein, Sadikov, Mishaeli et al., 2000) and cisplatin (Huguier, Barrier, Valinas et al., 2001; Andre, Balosso, Louvet et al., 2000; Kornek, Schratte-Sehn, Marczell et al., 2000; Andre, Lotz, Azzouzi et al., 1996) resulted in an improvement in the natural course of pancreatic cancer.

Weekly 5-FU with leucovorin, daily dipyridamole and intermittent mitomycin-C was reported to be effective palliative, neoadjuvant and adjuvant chemotherapy for pancreatic cancer (Chakravarthy, Abrams, Yeo et al., 2000; Burch, Ghosh, Schroeder et al., 2000; Todd, Gloor, Lane et al., 1998). Early survival analysis by Chakravarthy et al., suggested a trend toward increased median disease-free survival (8.3 vs. 17 months) using the same protocol as an adjuvant chemotherapy (Chakravarthy, Abrams, Yeo et al., 2000). In the study of Burch et al., 9 partial responses and 1 complete tumor response were seen out of 46 evaluable patients of unresectable pancreatic cancer (Burch, Ghosh, Schroeder et al., 2000). Todd et al reported a 39% response rate, 14 partial responses and one complete response out of 38 cases of unresectable pancreatic cancer (Todd, Floor, Lane et al., 1998).

Considering the encouraging results from the combination of anti-cancer drugs, we modified this chemotherapeutic protocol for pancreatic cancer and designed this pilot study. Five of six patients died of their disease following a 4.4 month period of disease
stabilization and a median survival of 8.9 months, which a promising result compared to
other series for pancreatic cancer. Furthermore, one patient exhibited a complete response
for more than 36 months documented by CT scanning, tumor markers and clinical
manifestations. In previous series, maximal one-year survival rates were 10-20% and
complete response and/or more than two-year survival was quite rare (Costanzo,
Tagliaventi, Carlini et al., 1996). In some clinical trials, some patients with unresectable
pancreatic cancer were reported to show long-term survival although the overall response
of the series was poor. It is unclear why some cases appear to be sensitive to chemotherapy,
whereas others are unresponsive. As the responder in this study showed no special
characteristics comparing to the other cases, the reason of the variable responses was also
unclear. The characteristics of pancreatic cancer may be varied and individualized, hence
chemotherapy should ideally be tailored to the individual patient based on the unique
characteristics of the disease. The detection of potentially chemotherapy-responsive
tumors would significantly improve the response rate of tumors and would facilitate the
selection of effective individualized regimens. This is a most important area of research in
the future.

In conclusion, the combination of 5-FU, leucovorin, and mitomycin-C is well
tolerated and justifies future comparative clinical trials which should incorporate
biochemical, histopathological and genetic techniques to examine why this drug regimen
may be more effective in some patients.

References

(cisplatin and 5-fluorouracil) as palliative treatment for localized unresectable or
adjuvant treatment for resected pancreatic adenocarcinoma: results of a feasibility


