Outcomes and Tolerability of Systemic Chemotherapy for Pancreatic or Biliary Cancer Patients Aged 75 Years or Older

Seigo Yukisawa1,*, Hiroshi Ishii1, Masato Matsuyama1, Kensuke Kuraoka1, Koichi Takano1, Akira Kamei1 and Masato Ozaka2

1Division of Hepatobiliary and Pancreatic Medical Oncology, Department of Gastroenterology, Cancer Institute Hospital and 2Division of Medical Oncology, Cancer Institute Hospital,Tokyo, Japan

*For reprints and all correspondence: Seigo Yukisawa, 3-8-31, Ariake, Koto-ku, Tokyo 135-8550, Japan.
E-mail: syukisawa@yahoo.co.jp

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Background: The incidence of pancreatic or biliary tract cancer is increasing in our aging population, but little is known of treatment outcomes in elderly patients with pancreatic or biliary tract cancer.

Patients and methods: Patients with pancreatic or biliary tract cancer who received chemotherapy in our institute between September 2007 and August 2009 were retrospectively reviewed to compare treatment outcomes between the elderly (aged 75 years or older) and the younger patients. Data were collected of patient backgrounds, adverse events and dose intensity within the first two cycles and overall survival time.

Results: Of the 102 who met the inclusion criteria, 19 were elderly who were introduced to full dose chemotherapy. Medication for their comorbidities was required in 15 (79%) of the 19 elderly patients and in 27 (33%) of 83 younger patients. The frequencies of haematological adverse events of grades 3 or 4 were 42% and 39%, and those of non-haematological adverse events were 21% and 16%, for the elderly and younger, respectively. Similar dose intensities were delivered to the elderly and younger. Also, similar proportions of elderly and younger received dose reductions. There was no difference in overall survival between the elderly and the younger.

Conclusion: No clear difference in treatment outcomes was seen between the elderly and the younger patients who received gemcitabine alone. Gemcitabine chemotherapy appears to be safe and the same treatment effect was seen even in older patients with pancreatic or biliary tract cancer.

Key words: elderly patients – pancreatic cancer – biliary cancer – chemotherapy

INTRODUCTION
Pancreatic or biliary tract cancer (PBCa) is known to have poor outcomes and advancing age has been associated with an increased incidence of this disease. Changing demographics in developed countries are characterized with the elderly comprising an increasing proportion of the population. This will result in a growing number of elderly patients with PBCa. In 1990, newly diagnosed pancreatic and biliary tract cancer patients aged 75 years or older showed incidences of 37% of 14,583 and 43% of 13,770 patients in Japan. However, in 2003, those numbers increased to 46% of 24,442 pancreatic cancer patients, and 58% of 11,401 biliary tract cancer patients (1). Despite the increased incidence of PBCa with age, elderly patients tend to be under-represented in clinical trials (2,3). Most clinical trials have excluded elderly patients because of the progressive reduction of organ function and co-morbidities related to age. Accordingly, only a small fraction of elderly patients have been entered into clinical trials. Hutchins reported that there was a substantial under-representation of patients 65 years of age or older in studies of treatment for cancer (4). As for lung cancer, some prospective trials showed the benefit of chemotherapy for elderly patients (5–7). However, only scant data are available among elderly patients with PBCa. Therefore, it is not known whether elderly patients...
with PBCa can tolerate standard full-dose chemotherapy regimens and result in outcomes similar to those seen in younger patients. Because of this lack of evidence, chemotherapy has generally been excluded from the treatment options for elderly patients with advanced PBCa probably for the reasons that chemotherapy is never curative and has toxic effects.

To determine the safety and effectiveness of chemotherapy for elderly PBCa patients, we reviewed the data of patients who were treated at our institution.

PATIENTS AND METHODS

PATIENTS

 Patients were selected from our database with the following criteria: (i) radiologically confirmed pancreatic or biliary tract carcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder carcinoma, or ampullary carcinoma), (ii) histologically or cytologically proven adenocarcinoma, (iii) no prior anti-cancer chemotherapy for PBCa, (iv) chemotherapy with gemcitabine (Gem) alone initiated between September 2007 and August 2009 at the Cancer Institute Hospital. Elderly patients were defined as 75 years of age or older, and treatment outcomes were compared between the elderly and the other patients.

CHEMOTHERAPY

In clinical practice, we generally employed Gem alone as the front line chemotherapy for PBCa. Gem was delivered at a dose of 1000 mg/m² by intravenous infusion on days 1, 8 and 15 of a 4-week cycle. Indicators of consensus criteria of chemotherapy in our team included good performance status, adequate organ function and historical absence of serious cardiac or cerebral vascular disease or mental disorder. For elderly patients, no geriatric assessment scoring system was used but Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 was regarded as essential for chemotherapy. However, details of indicators or treatment management depended on each physician. In general, Gem was suspended to allow recovery from the following toxicities: neutrocyte count <1000/mm³, platelet count <70 000/mm³ or grade 3/4 non-haematologic toxicity.

ANALYSIS

Individual data were collected from all medical records of the study patients. This included the past medical history, present illness, documents of imaging diagnosis, laboratory data and adverse events within the first two cycles of chemotherapy, and status at the last visit. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Dose intensity was surveyed within the first two cycles for Gem monotherapy. Overall survival data was fixed on June 2010.

In the current study, the responses between the elderly (75 years or older) and the younger were subjected to statistical comparisons. This study protocol was approved by the institutional review board in Cancer Institute Hospital.

STATISTICAL ANALYSIS

Differences between the elderly and the younger were compared using the exact Wilcoxon test for numeric or ordinal variables, Fisher’s exact test for binary variables and likelihood ratio test for multi-category discrete variables. Two-sided P values <0.05 were considered to be statistically significant. Overall survival was measured from the date of the start of chemotherapy to the date of death or last follow-up. Survival curves were generated using the Kaplan–Meier method, and median survival times were reported with 95% confidence intervals.

All statistical analyses were performed using the SPSS statistical software program package (SPSS version 11.0 for Windows).

RESULTS

PATIENT AND TUMOUR CHARACTERISTICS

There were 102 PBCa patients who met the selection criteria (Table 1). Of the 102, 19 (19%) were elderly patients. The median ages were 78.0 years (range 75–85) and 65.3 years (range 41–74) for the elderly and younger patients, respectively. The ECOG PS at the baseline was either 0 or 1 in all of the patients. The median follow-up duration was 9.1 months. There were no significant differences for background data between the elderly and the younger patients.

COMORBIDITIES OF THE PATIENTS

The comorbidities of the patients are listed in Table 2. Of the 19 elderly patients, 15 (79%) had at least one...
comorbidity which needed some degree of medication. In contrast, comorbidities were seen in 27 of 83 (33%) younger patients. The proportion of the elderly with comorbidities was significantly higher than in the younger patients. Cardiovascular disease and diabetes mellitus were most frequently observed. Serum creatinine levels at the initiation of chemotherapy were under 1.5 mg/dl for all patients and severe renal dysfunction was not seen in the current study. Of the 19 elderly patients, there were 5 patients with medical history of cancer surgery: 3 with gastric cancer, 1 with breast cancer, and the remaining 1 with thyroid cancer. Of the 83 younger patients, there were 9 patients with history of cancer surgery: 1 with oesophageal cancer, 4 with gastric cancer, 3 with colorectal cancer, 2 with uterus cancer, and the remaining 1 with prostate cancer (1 with both gastric cancer and colorectal cancer).

**TOXICITIES**

Adverse events, for which grading resulted in the worst values were encountered within the first two cycles of treatment, and are reported in Table 3. Haematological toxicities of grades 3–4 were seen in 8 (42%) of the 19 elderly and in 32 (39%) of the 83 younger patients. Non-haematological toxicities occurred in 4 (21%) of the elderly, and in 13 (16%) of the younger patients. The number of any grade 3–4 toxicities was 8 (42%) in the elderly and 37 (45%) in the younger patients. Severe adverse events occurred in 1 (5%) of the elderly and in 9 (11%) of the younger patients.

Severe adverse event in the elderly patient was cholangitis due to progression of the original lesion and recovery was observed within a few days by biliary drainage. Most of the adverse events were also related to progression of PBCa. The number of patients who could not continue chemotherapy by two cycles due to adverse events was two (11%) in the elderly and eight (10%) in the younger patients. The frequencies of any of the grade 3–4 toxicities and severe adverse events were not significantly different between the elderly and the younger patients.

### Table 2. Summary of comorbidities of the patients

<table>
<thead>
<tr>
<th>Comorbidities (medication)</th>
<th>≥75</th>
<th>&lt;75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old cerebral infarction</td>
<td>1 a</td>
<td>0</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 b</td>
<td>20 c</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatic aoritis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>1 d</td>
<td>1</td>
</tr>
<tr>
<td>Inhaler use</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Insulin use</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Oral administration</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
| Total cases (%)                  | 15 (79%) | 27 (33%) | *P* < 0.001

The numbers refer to patients who had one or more comorbidities. Of 19 elderly patients, 8 patients had one, 6 had two and 1 had three kinds of comorbidities.

1 The patient also used antihypertensive drug.
2 Five patients also used diabetes drugs.
3 Nine patients also used diabetes drugs.
4 The patient also used antihypertensive drug and diabetes drugs.

Of 83 younger patients, 15 patients had one and 12 had two kinds of comorbidities.

### Table 3. Summary of grades 3–4 toxicity in the elderly (aged 75 years or older) and the younger (under 75 years)

<table>
<thead>
<tr>
<th>No. of events</th>
<th>≥75</th>
<th>&lt;75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6</td>
<td>49</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>
| Total (Haematological AE) cases (%) | 8 (42%) | 32 (39%) | *p* = 0.61
| Lethargy      | 2   | 6   |
| Infection (non-neutropenic) | 1 cholangitis | 5 cholangitis
| Bilirubin     | 0   | 2   |
| Transaminases | 3   | 10  |
| Gastrointestinal | 0 | 1 ascites
| 1 ileus       |     |     |
| Diarrhoea     | 0   | 1   |
| Renal         | 0   | 0   |
| Pulmonary     | 0   | 1   |
| Others        | 0   | 1   |
| Total (non-haematologic AE) cases (%) | 4 (21%) | 13 (16%) | *p* = 0.77
| Total (all AE) cases (%) | 8 (42%) | 37 (45%) | *p* = 1.00

Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria version 3.0.
DOSE INTENSITY

Similar dose intensities (538 mg/m² per week to the elderly and 596 mg/m² per week to the younger) were delivered within the first two cycles of GEM chemotherapy. The dose of Gem within the first two cycles was reduced in five (26%) of the elderly and in 20 (24%) of the younger patients.

OVERALL SURVIVALS

Regarding the 102 patients with unresectable tumours who received Gem alone, 11 patients survived, 70 died and the remaining 21 were censored mainly because they changed hospitals at the time when we fixed the data in June 2010. The median overall survival days were 308 (95% CI: 130–486) and 315 (95% CI: 232–398) days in the elderly and younger patients, respectively (Fig. 1). There was no statistical difference between the two groups ($P = 0.340$).

DISCUSSION

With the increasing life expectancy of the overall population in Japan, there has also been a rise in the number of elderly cancer patients. Because of comorbidities or age itself, the deterioration in organ function is seen more frequently in the elderly, compared with the younger patients. Therefore, consideration of treatment feasibility needs special attention for the elderly cancer patients. A less toxic regimen has been tried, in particular, for advanced-staged lung cancer or haematological malignancies (5–7). The current study was conducted to examine the feasibility and effectiveness of chemotherapy for elderly PBCa patients because of lack of knowledge on this issue.

To date, either Gem or fluoropyrimidine has been a key drug for PBCa. Gem has been widely used as a standard chemotherapeutic agent for advanced PBCa. Especially in pancreatic cancer, Gem alone still remains as the standard regimen both in the adjuvant setting after surgery and in treatment of advanced disease.

Gem is thought to be less toxic than other cytotoxic agents, such as platinum or taxans (8), which showed grades 3–4 haematological and non-haematological adverse events of 10–24% and 20–50% (9–11), respectively. Therefore, special attention may not be necessary to perform Gem chemotherapy for the elderly. In fact, the current study demonstrated that full-dose chemotherapy with Gem for PBCa was feasible in the younger as well as the elderly patients. The favourable results seen for the elderly in the current study may be attributed to good patient selection. Special emphasis was placed on performance status rather than comorbidities.

Marechal et al. (12) also pointed out the importance of performance status when considering chemotherapy for elderly patients with pancreatic cancer.

Recently, a consensus has been achieved for Gem in combination with cisplatin as the standard regimen for biliary tract cancer based on results of ABC-02 (11) and BT22 trials (10). For chemotherapy with cisplatin, hydration is commonly recommended to reduce renal toxicity. Cisplatin is thought to be difficult to adapt elderly patients with cardiac and/or renal disease at baseline. Accordingly, another platinum agent such as carboplatin or nedaplatin is often employed for lung or oesophageal cancer chemotherapy regimen as an alternative to cisplatin for the treatment of elderly patients. In both ABC-02 and BT22 trials, cisplatin was delivered at low (25 mg/m²) and fractional (days 1 and 8 of a 3-week cycle) doses. This might lead to low-frequency renal toxicity (1.5%, with grades 3–4 renal adverse events) (11). Despite low toxicity, whether the combination of Gem and cisplatin is an appropriate option for the elderly patients needs to be validated because cisplatin will be approved by the Japanese government in the near future.

The toxicities of chemotherapy were evaluated only for two cycles. Late-onset adverse effects might occur especially in elderly patients due to deterioration of organ function. Unquestionably, adverse effects for the elderly need to be monitored carefully during all courses of chemotherapy. However, in view of the lack of a consensus of dose setting, our data support the use of first-line Gem for PBCa by the full-dose setting.

In conclusion, our data shows that old age is not a contraindication to full-dose chemotherapy with Gem for PBCa. Gem monotherapy appears to be safe and delivers the same treatment effect even in older patients with PBCa. Chemotherapy using Gem can be applied to elderly patients as well as younger patients, if those patients with well-
preserved physical status and organ functions are appropriately selected.

Conflict of interest statement
None declared.

References