Irinotecan Plus Cisplatin for Therapy of Small-cell Carcinoma of the Esophagus: Report of 12 Cases from Single Institution Experience

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Background: Esophageal small-cell cancer is a rare disease, and standard therapy has not yet been established.

Methods: A total of 12 esophageal small-cell carcinoma patients were treated with CPT-11 (70 mg/m²) on Days 1 and 15 and CPT-11 plus CDDP (80 mg/m²) on Day 1 with each cycle repeated every 4 weeks at our institution.

Results: A total of 46 chemotherapy courses were given (median, 3.5). There were two complete responses and eight partial responses. The median survival time was 417 (97–1626) days, and three patients were still alive for more than 40 months. Grade 4 neutropenia was observed in two patients, Grade 4 anemia in one patient, Grade 3–4 diarrhea in three patients and Grade 3–4 hyponatremia in three patients. Other adverse reactions seen were mild with no treatment-related deaths observed.

Conclusions: To our knowledge, this is the first report of the series of more than 10 patients with small-cell carcinoma of the esophagus treated with the same chemotherapy regimen. The combination of CPT-11 and CDDP appears to be effective therapy of this disease with acceptable toxicity profile. We believe that this regimen is one of the options to be considered for treatment of esophageal small-cell carcinoma.

Key words: small-cell carcinoma – esophageal cancer – chemotherapy – CPT-11 – cisplatin

INTRODUCTION

Esophagus is one of the sites of extrapulmonary occurrence of the small-cell carcinoma. In the gastrointestinal (GI) tract, ~50% of tumors arise in the esophagus (1). Small-cell esophageal cancer (SCEC) is a rare disease with aggressive behavior and poor prognosis. Because of the rarity of this disease, standard therapy has not yet been established. Systemic chemotherapy is offered to patients with metastatic disease where chemoradiation or surgery is used to manage locoregional disease. Small-cell carcinoma is considered to be highly sensitive to chemotherapy. Since SCEC has similar histological and clinical characteristics to the small-cell lung cancer (SCLC), the same therapeutic strategies for both malignancies are recommended in the literature (2–5).

Irinotecan hydrochloride (CPT-11) has demonstrated activity against various tumor histologies. Marked synergism, lack of cross-resistance, different mechanisms of action, and different toxicity profiles make the combination of CPT-11 with cisplatin (CDDP), an attractive regimen (6). Phase II studies investigated this combination in therapy of SCLC and gastric cancer, demonstrating good efficacy with acceptable toxicity profile (7,8). Phase III evaluation of CPT-11 and cisplatin provided improved progression-free survival and overall survival (OS) in patients with metastatic SCLC compared with the etoposide and cisplatin combination regimen (9). Therefore, at our institution, we use CPT-11/ CDDP combination to treat SCEC. We report here the results of our experience with 12 cases.

MATERIALS AND METHODS

Fifteen out of 631 esophageal cancer patients were diagnosed between June 1999 and May 2004 at the Cancer Institute Hospital of Japanese Foundation for Cancer
Research as small-cell carcinoma pathologically (2.4%). We used immunohistochemical staining for neuron-specific enolase, CD56, chromogranin A, synaptophysin and so on in diagnosis for small-cell carcinoma of the esophagus. Out of these 15 patients, 12 were treated with CPT-11 plus CDDP. We conducted retrospective medical records review of the 12 cases. Staging evaluation included computed tomography (CT) of the chest, abdomen, barium esophagography and esophagoscopy with biopsy. We applied the tumor-node-metastasis (TNM) staging system to all cases according to the International Union against Cancer (UICC) classification. Since primary extrapulmonary sites of the small-cell carcinoma are rare, a primary SCLC should be excluded. In our patients, primary SCLC was excluded in each case, using CT evaluation of the chest.

TREATMENT SCHEDULE
Chemotherapy regimen was applied as follows: on Day 1, CPT-11 (70 mg/m²) was administered by intravenous infusion over 90 min; this was followed by a 2-h interval after which, intravenous infusion of CDDP (80 mg/m²) was administered over 2 h with adequate hydration. The same dose of CPT-11 was administered on Day 15. This regimen was repeated every 4 weeks until disease progression, patient refusal or unacceptable toxicity has occurred.

RESPONSE EVALUATION
For measurable disease, responses were evaluated according to the World Health Organization (WHO) criteria (10). Response for the primary tumor was also evaluated according to the modified criteria of the Japanese Society for Esophageal Disease (11). Briefly, complete response (CR) for a primary tumor was consistent with disappearance of all visible tumors including ulceration and negative biopsy result on esophagography that lasted more than 4 weeks. Partial response (PR) was assigned if the primary tumor was reduced by >50% on esophagography and lasted for >4 weeks. Progressive disease (PD) was consistent with an increase in the tumor area by >25%. Responses were evaluated using esophagography, esophagoscopy and CT of the chest and abdomen. The National Cancer Institute-Common Toxicity Criteria (NCI-CTC; version 2.0) was used to evaluate observed toxicity.

STATISTICS
Survival was measured from the date of the start of CPT-11/CDDP chemotherapy until death or the most recent follow-up visit. Survival data were estimated using Kaplan–Meier method.

RESULT
PATIENT CHARACTERISTICS
Patient characteristics are listed in Table 1. Out of 12 patients, only one patient was female. The age ranged between 53 and 77 years with a median age of 66 years. Ten patients (83%) had performance status (PS) 0–1 with two treated patients with PS of 2. The tumor was located in the middle third of the esophagus in seven patients. The median size of the primary tumor was 6.0 cm. Histologically, four out of 12 (33%) tumors were of mixed small-cell and squamous cell histology with remaining eight tumors of only small-cell type (67%) by biopsy. Five patients had locoregional disease and remaining seven patients with either metastatic or recurrent tumor after surgical resection.

One patient had previous history of gastric adenocarcinoma 8 years prior to the diagnosis of small-cell cancer of the esophagus. Another patient had simultaneously detected advanced gastric adenocarcinoma and esophageal small-cell cancer.

Ten out of 12 patients (83%) had no prior treatment for their malignancy. One patient (Patient 6) received 2 Gy of radiation to esophageal tumor prior to chemotherapy. Radiation was started initially as he was thought to have squamous cell carcinoma of the esophagus. However, few days later his histology report was amended to add the small-cell component. In another patient (Patient 11), pharyngeal mass was noted 3 months after esophagectomy. Because, at first, it was clinically diagnosed as second primary-pharyngeal cancer, 4 Gy of radiation to pharyngeal tumor was applied.

TREATMENT
The total number of chemotherapy courses given was 46 (median, 3.5 courses per patient; range, 2–6 courses) (Table 2). In three patients, 20–25% dose reduction of both agents was needed at first cycle due to the old age (Patient 1), borderline PS (Patient 4) or proximity of the last radiotherapy session (Patient 11). Additional two patients required both omitting Day 15 of CPT-11 in the first course and dose reduction following the first cycle due to the diarrhea, neutropenia or hyponatremia. Seven out of 12 patients were able to receive planned full doses of chemotherapy for all cycles.

RESPONSE AND SURVIVAL
There were two CRs and eight PRs achieved resulting in a response rate (RR) of 83%. The RR of primary esophageal lesion was 82% (nine of 11 patients) (Table 2). The median follow-up time was 462 days, and the median survival time of all patients was 417 days (range, 97–1626 days) (Figure 1). Three patients (Patients 2, 9 and 12) were still alive at the last follow-up, for over 40 months. Two had locoregional disease and one had metastatic disease. Two (Patients 2 and 9) of the three patients showed no evidence...
of disease. One patient (Patient 9) developed recurrent
disease at the primary site at 24 months after initial CR, but
it disappeared again with chemotherapy (nedaplatin and
5-FU) followed by radiation. Since, initially, she had bulky
lymph node metastasis in her neck, we performed enough
chemotherapy again followed by radiation despite local
recurrence only. Two (Patients 2 and 12) of the three alive
patients underwent additional concurrent chemoradiotherapy
following second and third course of irinotecan and cisplatin
because residual tumor after this chemotherapy (Patient 12)
and to ensure disease control in spite of disappearance the
tumor (Patient 2). These subsequent therapies included a
total of 50 and 60 Gy, respectively, of radiation and combi-
nation of cisplatin and 5-fluorouracil. One patient (Patient
12) achieved complete response after chemoradiation, and
recurrent neuroendocrine carcinoma with squamous cell
differentiation was detected in lung at 35 months from the
start of chemotherapy. Because there was a possibility of
primary lung cancer, it was surgically resected. At 40
months, metastasis was found again in the lung and pleura,

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>PS</th>
<th>Gross type</th>
<th>Stage</th>
<th>Site of primary esophageal tumor</th>
<th>Tumor length (cm)</th>
<th>Metastatic site</th>
<th>Previous treatment</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>77</td>
<td>0</td>
<td>Polyploidy</td>
<td>4b</td>
<td>Middle third</td>
<td>9</td>
<td>Liver LN</td>
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<td>2</td>
<td>M</td>
<td>69</td>
<td>1</td>
<td>Ulcerative</td>
<td>2</td>
<td>Lower third</td>
<td>5</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>62</td>
<td>1</td>
<td>Ulcerative</td>
<td>3</td>
<td>Middle third</td>
<td>6</td>
<td>mLN</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>59</td>
<td>2</td>
<td>Ulcerative</td>
<td>4b</td>
<td>Lower third</td>
<td>13</td>
<td>cLN, mLN, aLN, pleural effusion</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>66</td>
<td>1</td>
<td>Ulcerative</td>
<td>4a</td>
<td>Upper third</td>
<td>7</td>
<td>mLN, cLN</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>53</td>
<td>2</td>
<td>Ulcerative</td>
<td>4b</td>
<td>Middle third</td>
<td>5</td>
<td>cLN, mLN, pleural effusion</td>
<td>RT(2Gy)</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>66</td>
<td>1</td>
<td>Ulcerative</td>
<td>4b</td>
<td>Lower third</td>
<td>6</td>
<td>cLN, mLN, aLN</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>70</td>
<td>0</td>
<td>Polyploidy</td>
<td>3</td>
<td>Middle third</td>
<td>4</td>
<td>mLN</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>63</td>
<td>1</td>
<td>Ulcerative</td>
<td>4b</td>
<td>Middle third</td>
<td>8</td>
<td>cLN</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>71</td>
<td>0</td>
<td>Ulcerative</td>
<td>4b</td>
<td>Middle third</td>
<td>9</td>
<td>mLN, adrenal gland</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>61</td>
<td>1</td>
<td>NE recurrence</td>
<td></td>
<td>NE</td>
<td>NE</td>
<td>Pharynx</td>
<td>Esophagectomy, RT(4 Gy)</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>68</td>
<td>0</td>
<td>Polyploidy</td>
<td>1</td>
<td>Middle third</td>
<td>3</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

LN, lymph node; cLN, cervical LN; mLN, mediastinal LN; aLN, abdominal LN; RT, radiation; NE, not evaluated; PS, performance status; M, male; F, female.

Table 2. Treatment course and results of treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total course of Cx</th>
<th>Response</th>
<th>Oral food intake</th>
<th>PD site</th>
<th>Survival (days)</th>
<th>Subsequent therapy</th>
<th>Present status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>PR</td>
<td>Semi-solid</td>
<td>Solid</td>
<td>Esophagus, LN</td>
<td>RT</td>
<td>Dead of disease</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>CR</td>
<td>Solid</td>
<td>Solid</td>
<td>Non-PD</td>
<td>5-FU + CDDP + RT</td>
<td>Alive with NED</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>PR</td>
<td>Semi-solid</td>
<td>Solid</td>
<td>Esophagus</td>
<td>RT</td>
<td>Dead of disease</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>PR</td>
<td>Liquid</td>
<td>Solid</td>
<td>LN</td>
<td>docetaxel</td>
<td>Dead of disease</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>PD</td>
<td>Semi-solid</td>
<td>Semi-solid</td>
<td>Esophagus</td>
<td>RT</td>
<td>Dead of disease</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>PR</td>
<td>Semi-solid</td>
<td>Semi-solid</td>
<td>Pleural effusion</td>
<td>none</td>
<td>Dead of disease</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>PD</td>
<td>Liquid</td>
<td>Semi-solid</td>
<td>Esophagus, LN, adrenal gland</td>
<td>RT</td>
<td>Dead of disease</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>PR</td>
<td>Semi-solid</td>
<td>Semi-solid</td>
<td>LN</td>
<td>MTX/5-FU</td>
<td>Dead of disease</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>CR</td>
<td>Semi-solid</td>
<td>Semi-solid</td>
<td>Non-PD</td>
<td>nedaplatin + 5-FU</td>
<td>Alive with NED</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>PR</td>
<td>Solid</td>
<td>Solid</td>
<td>Pancreas</td>
<td>5-FU + CDDP + RT</td>
<td>Dead of disease</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>PR</td>
<td>NE</td>
<td>NE</td>
<td>LN</td>
<td>RT</td>
<td>Dead of disease</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>PR</td>
<td>Solid</td>
<td>Solid</td>
<td>Non-PD</td>
<td>5-FU + CDDP + RT</td>
<td>Alive with disease</td>
</tr>
</tbody>
</table>

CPT-11 and CDDP is effective for SCEC
and then he was treated with nedaplatin and 5-FU. There was no recurrence at the primary site at 4-year follow-up. A patient (Patient 3) with stage III SCEC obtained PR with CPT-11 plus CDDP, which was continued until PD in the primary site. He received radiation alone following CPT-11 plus CDDP, but did not get reduction of primary tumor or improvement of dysphagia and developed new lesion in abdominal lymph nodes.

ASSESSMENT OF ORAL INTAKE

We also assessed oral intake in our patients which was categorized as follows: patient can ingest solid food, semi-solid food, only liquid or neither food nor liquid.

We evaluated 11 patients for changes in their oral intake before and after treatment (Table 2). After treatment, five out of these eight patients achieved improvement in oral intake.

ADVERSE REACTIONS

Toxicity of this regimen is summarized in Table 3. The most frequent adverse reaction was nausea/vomiting and diarrhea. Grade 3–4 nausea was observed in two patients (17%) with Grade 3–4 diarrhea noted in three patients (25%). Diarrhea was controlled with loperamide or other antidiarrheals, and supported with intravenous hydration.

Grade 3–4 hyponatremia was observed in three patients (25%) with Grade 3–4 neutropenia in seven patients (58%) including one Grade 4 (8%) with Grade 3–4 infection documented in two patients (17%). Other hematologic adverse reactions were mild with no treatment-related deaths observed.

DISCUSSION

Since McKeown reported first two cases of small-cell carcinoma of the esophagus (12), there have been only <300 cases this disease described in the literature (1). It comprises only 0.8–2.4% of all esophageal malignancies (13). In our hospital, there were 15 patients diagnosed with this disease out of 631 of all identified esophageal malignancies between June 1999 and May 2004. This makes our institutional incidence rate of 2.4% that is consistent with the rate reported in the literature. Because of the rarity of this disease, the standard treatment has not yet been established. Many investigators recommend that SCEC should be managed similar to SCLC (2–5). A randomized phase III study was conducted in Japan comparing the combination of CPT-11 and CDDP with standard regimen for extensive stage SCLC: etoposide plus cisplatin. The median survival was 12.8 months in the CPT-11 plus CDDP arm and 9.4 months in the etoposide plus cisplatin group (P = 0.002 by the unadjusted log-rank test) (9). Those results demonstrated efficacy of CPT-11/CDDP in therapy of advanced SCLC.

Reports of a single case have suggested that CPT-11/CDDP combination was also effective in SCEC (14,15). In our experience of 12 cases, CPT-11 plus CDDP demonstrated RR of 83% (10 of 12 patients) with median survival of 417 days (13.9 months) and three patients were still alive for over 40 months. Three out of seven patients with metastatic or recurrent disease survived for >10 months.

Limited stage SCLC is usually treated with concurrent chemoradiotherapy. Because of aggressive behavior, we initially treated local disease of SCEC also with CPT-11 plus CDDP. After that, four of five patients with locoregional disease received radiation (including two concurrent chemoradiation). Two patients (Patients 3 and 5) received radiation without chemotherapy after failure in CPT-11 plus CDDP.
For another local disease patient (Patient 8), we did not use radiation due to progression of simultaneously detected advanced gastric cancer. Three long survivors (Patients 2, 9, 12) all received subsequent radiotherapy after this CPT-11 plus CDDP chemotherapy (Table 2). One (Patient 12) of them achieved complete response after chemoradiation, and there has been no evidence of recurrence at the primary site for >40 months. Another patient (Patient 9) developed recurrent disease at the primary site, and disappeared again using sequential chemotherapy followed by radiation. Therefore, it is thought that this chemotherapy alone is not enough and radiotherapy is needed to obtain CR in the primary site. Takada et al. showed that concurrent chemoradiotherapy group was superior to sequential group for limited stage SCLC (16). Two patients with local disease (Patients 3 and 5) who received radiation without chemotherapy after failure in CPT-11 plus CDDP did not get reduction of primary tumor. It is considered that concurrent chemoradiation is better than sequential in SCEC also and used before progression of the disease. The appropriate chemotherapy concurrently with radiotherapy for SCEC is unknown. We used combination of 5-FU plus cisplatin concurrently because some tumors were of mixed small-cell and squamous cell histology. Several studies demonstrated the promising efficacy of chemoradiotherapy concurrently with etoposide plus cisplatin (16,17), which is an attractive treatment for locoregional SCEC. Since there has been no adequate data on safety and efficacy of concurrent CPT-11 and radiation applied to the mediastinum, we did not use it in our patients. We would like to point out that CPT-11 plus CDDP chemotherapy used alone was able to induce CR in two patients. Nine out of 11 patients demonstrated CR or PR in primary esophageal tumor. Additionally, oral intake tolerance was improved in majority of treated patients (five of eight patients). These data suggest that CPT-11 plus CDDP chemotherapy is a good treatment as induction chemotherapy and subsequent chemoradiation are necessary for locoregional disease of SCEC.

Several retrospective reviews reported poor prognosis of SCEC. However, these patients were not treated with the same chemotherapy regimen and various initial treatments including surgery or radiation were applied. Casas et al. (18) reported literature review of 230 patients with SCEC (199 evaluable patients). In this report, median survival for patients with local disease was 8 months and extensive disease patients surviving only 3 months. Bennouna et al. (19) presented 10 cases of SCEC treated with various cisplatin-based chemotherapy regimens. Complete response was observed in eight patients. Seven of these patients received subsequent locoregional radiotherapy with endoesophageal brachytherapy applied in two patients. The overall median survival for all patients was 15.5 months (range, 2–36 months). In limited disease, the median survival was 18.5 months (range, 2–36 months) with 11 months (range, 6–19 months) median survival seen in patients with extensive disease.

Medgyesy et al. (20), at the University of Texas, M. D. Anderson Cancer Center, reported with eight cases of SCEC that four out of six patients with limited stage disease received combined modality treatment including esophagectomy and two received only radiotherapy. Two patients with extensive disease were treated with chemotherapy alone. Observed median OS in this report was 12.5 months (range, 5–57 months). Some authors suggested that surgery is a possible choice of treatment for SCEC (20,21). Surgery considered being also an alternative method for local control instead of chemoradiation.

In our experience, four out of seven patients with metastatic or recurrent disease survived for more than 10 months (range, 3–43 months). Four out of five patients with local disease survived for more than 1 year (range, 10–54 months). This statistics is comparable, or better, with data reported in the literature.

Diarrhea and neutropenia are major toxicities of CPT-11 and CDDP. Neutropenia occurred in 11 of 12 patients (92%) following the first cycle. Grade 4 neutropenia was observed in two of 12 patients (17%) and Grade 3 or 4 diarrhea occurred in three of 12 patients (25%) during all courses; however, both toxicities were well controlled with the use of G-CSF and loperamide, respectively. These observed side effects are comparable with toxicity data reported in the literature. SIADH was seen in one of our patients and it was of brief duration. All severe adverse reactions were manageable and did not recur after 20–25% dose reduction in subsequent courses. There was no treatment-related death observed. Therefore, we consider this regimen to be safe and tolerable in patients with SCEC.

To date, there are only few single-center, retrospective reports published in the literature on experience with therapy of the esophageal small-cell cancer. We believe our report is the first to comment on treatment of more than 10 small-cell esophageal carcinoma patients using the same chemotherapy regimen. Our overall RR achieved with this therapy was 83%, including two complete responses, with median survival time of 417 days. This is comparable with data reported in the literature. Although the small number of patients prohibits any firm conclusions, we believe that this regimen is one of the options to be considered for initial treatment of this disease.

Conflict of interest statement
None declared.

References