Novel treatment (new drug/intervention; established drug/procedure in new situation)

Small cell carcinoma of gastro-oesophageal junction with remarkable response to chemo-radiotherapy

Mototsugu Matsunaga,¹ Keisuke Miwa,¹ Tsuyoshi Noguchi,² Yasutsuna Sasaki¹

¹Department of Medical Oncology, International Medical Center, Comprehensive Cancer Center, Saitama Medical University, Hidaka, Japan

²Department of Surgical Division, Faculty of Medicine, Center for Community Medicine, Oita University, Oita, Japan

Correspondence to Dr Mototsugu Matsunaga, mmandmacgyver@yahoo.co.jp

Summary

Small cell carcinoma of the gastrointestinal tract is rare, and no effective strategy has yet been established. On the basis of regimens reportedly effective for small cell lung cancer, we performed chemotherapy with cisplatin plus etoposide in combination with radiotherapy to relieve obstruction, in a patient with small cell carcinoma of the gastro-oesophageal junction. Chemotherapy was switched to carboplatin plus etoposide due to renal toxicity. No distant metastases were detected and lesion spread was limited. A complete response, with no evidence of recurrence to date, was achieved. Curative resection was suggested but refused by the patient. He has been closely followed up in our outpatient clinic for more than a year and has shown no evidence of recurrence since the completion of treatment. Although cisplatin plus etoposide is a standard chemotherapy regimen for small cell carcinoma, carboplatin plus etoposide may be effective in cases in which cisplatin is contraindicated due to renal toxicity.

BACKGROUND

Small cell carcinoma of the gastrointestinal tract is uncommon, and occurrence in the gastro-oesophageal junction is particularly rare. Patients with small cell carcinoma generally have a poor prognosis, regardless of the primary tumour origin. The mean survival of patients with small cell carcinoma of the oesophagus is reportedly about 5 months due to comparatively high malignancy and a tendency for early vascular invasion, distant metastases and local recurrences.¹ Optimal treatment strategies for small cell carcinoma originating from the gastrointestinal tract have not, however, been adequately explored because of the small number of such patients. Consequently, no well-established treatment regimen currently exists. In this study, based on regimens that have been reported to be effective for small cell lung cancer, we performed chemotherapy with cisplatin (CDDP) plus etoposide (ETP, VP-16) in combination with radiotherapy in a patient with small cell carcinoma of the gastro-oesophageal junction. During the course of treatment, CDDP was changed to carboplatin (CBDCA) due to renal toxicity caused by CDDP. Otherwise, no serious adverse events were noted and the planned treatment was completed. The patient achieved a complete response (CR) and has shown no evidence of recurrence to date.

Herein, we report a case of small cell carcinoma of the gastro-oesophageal junction showing a remarkable response to chemo-radiotherapy (CRT) with a review of the relevant literature.

CASE PRESENTATION

A 73-year-old man presented to a neighbourhood hospital with a 1-month history of dysphagia. He was found to have a tumour in the gastro-oesophageal junction measuring a few centimetres in diameter on upper gastrointestinal endoscopy and was referred to the Department of

Gastrointestinal (Digestive Tract) and General Surgery at Saitama Medical University Hospital for further evaluation and treatment. Detailed examination revealed that the tumour to be a small cell carcinoma of the gastro-oesophageal junction. Radical surgical resection was contemplated but not undertaken since the presence of small cell carcinoma in the gastro-oesophageal junction is not an indication for curative surgery. He was referred to the Department of Medical Oncology for chemotherapy.

At the time of referral, he had difficulty in swallowing food, was barely able to take liquids and had received intravenous infusions for nutritional support since the time of hospital admission. However, he reported no other subjective symptoms and had an Eastern Cooperative Oncology Group (ECOG) performance status of 1, which is indicative of fairly good general condition.

His medical and family histories were unremarkable. He had no history of smoking and reported only occasional alcohol consumption.

INVESTIGATIONS

Blood biochemistry was normal on admission. Tumour markers, including carcinoembryonic antigen, cancer antigen 19-9 and pro-gastrin-releasing peptide, were within the normal ranges. Only neuron-specific enolase (NSE) was elevated (44 ng/ml).

Upper gastrointestinal endoscopy (before treatment) showed a huge tumour measuring ~10 cm in diameter that occupied the gastro-oesophageal junction from the lower oesophagus to the upper part of the lesser curvature of the gastric corpus (figure 1A,B). The centre of the tumour was necrotic and appeared to be soft. Although the tumour caused stenosis of the lumen of the gastro-oesophageal junction, an endoscope could barely pass through the stenotic area. A few biopsy samples were taken from the site of stenosis during endoscopy and all

Figure 1 Upper gastrointestinal endoscopic findings before treatment: (A) a tumour occupied the gastro-oesophageal junction and (B) retroflexed endoscopic view of a tumour of the gastro-oesophageal junction.

were subsequently diagnosed as harbouring small cell carcinoma.

Positron emission tomography (PET)/CT examinations (before treatment) revealed wall thickening and enhanced fluorodeoxyglucose (FDG) accumulation at the gastro-oesophageal junction, which correlated with the endoscopic findings (figure 2A,B). Lymph node hypertrophy was observed in the lesser curvature side of the junction, while no metastases to other organs, including the liver and lungs, were detected.

Histological findings (not shown): Biopsy samples from the tumour located in the gastro-oesophageal junction showed atypical cells staining positive for AE1/AE3, indicative of the presence of differentiated epithelium. Microscopic examination revealed small cells with high N/C ratios, some spindle-shaped, which were positive for CD56, chromogranin and synaptophysin on immunohistochemical analysis. More than 20% of the cells expressed Ki67 and none showed a CD3/CD20 pattern. Endoscopically, the tumour needed to be differentiated from lymphoma, although its immunohistochemical profile was negative for lymphoma markers.

DIFFERENTIAL DIAGNOSIS

According to the pathological response, the diagnosis was small cell carcinoma of the gastro-oesophageal junction.

Using the 2010 WHO Classification of Tumours of the Digestive System,² the tumour was pathologically classified as a small cell neuroendocrine carcinoma (NEC, small cell type).

TREATMENT

Since there is no well-established standard of care for small cell carcinoma of the gastro-oesophageal junction, we planned a regimen based on those for limited-disease (LD) small cell lung cancer. An enterostomy was performed in the Department of Gastrointestinal (Digestive Tract) and General Surgery prior to the initiation of CRT because the patient was unable to take anything by mouth. In consultation with the Department of Radiation Oncology, radiation therapy (a total dose of 40 Gy in 20 fractions) was scheduled and started simultaneously with chemotherapy with CDDP plus ETP (for up to four courses). The CDDP plus ETP regimen consisted of four 3-week cycles of 100 mg of ETP per square metre on days 1, 2 and 3 and 60 mg of CDDP per square metre on day 1. At completion of the first course of CDDP plus ETP, renal toxicity was observed. Consequently, CDDP was changed to CBDCA (AUC5) and chemotherapy was continued. At the completion of radiotherapy and the second course of chemotherapy, a marked reduction in tumour volume was observed and the patient resumed oral intake

Figure 2 Positron emission tomography/CT findings before treatment: (A) wall thickening of the gastro-oesophageal junction and lymph node hypertrophy can be seen on the lesser curvature side of the stomach and (B) an enhanced fluorodeoxyglucose accumulation is apparent.

Figure 3 Upper gastrointestinal endoscopy findings after treatment: (A) the tumour was not visible from the oesophagus side. (B) Retroflexed endoscopic view of the tumour. An ulcer scar was observed in the gastric side of the gastro-oesophageal junction. Marked reduction in tumour volume was observed when compared with the tumour volume observed before treatment.

without incident. Additional two courses of CBDCA plus ETP regimen were administered. Endoscopic examination performed at the completion of four courses of chemotherapy revealed no findings suggestive of oesophagitis, the tumour volume reduction in the gastro-oesophageal junction was maintained, and regression of tumour invasion to the oesophageal side was documented (figure 3A,B). There was a shallow ulcer scar on the gastric side of the gastro-oesophageal junction, which was later pathologically classified as Group 1 according to the group classification of gastric biopsy specimens by the Japanese Gastric Cancer Association, with no findings suggestive of malignancy. A PET/CT scan conducted around the same time showed disappearance of both wall thickening of the gastro-oesophageal junction and lymph node hypertrophy at the lesser curvature of the stomach (figure 4A,B). In addition, enhanced FDG accumulation found before treatment was no longer observed. The NSE elevation noted before CRT had decreased to within the normal range. On the basis of these results, we concluded that CRT was very effective and that the patient had achieved a CR. The tumour showed a marked response to CRT and there were no distant metastases. Thus, surgical resection became a possible therapeutic option. Curative surgery is not, however, well established for the treatment of small cell carcinoma of the gastro-oesophageal junction and the patient did not

give consent for surgery. Consequently, surgery was not performed.

OUTCOME AND FOLLOW-UP

The patient achieved a CR and has been closely followed up in the outpatient clinic. He has shown no evidence of recurrence for more than a year since the completion of CRT.

DISCUSSION

Neuroendocrine tumour originating in the gastrointestinal tract is a term referring to tumours with predominant neuroendocrine differentiation arising in the digestive tract. According to the 2010 WHO Classification System, such tumours can be classified into three major categories: neuroendocrine tumour (NET) Grade 1, NET Grade 2, and NEC (small cell type or large cell type).² In the present patient, the tumour was pathologically diagnosed as small cell carcinoma (NEC, small cell type) of the gastro-oesophageal junction.

Small cell carcinoma is a common pulmonary neoplasm, but has also been described in the oesophagus, stomach, pancreas, colon, rectum, small intestines, etc. Essentially, small cell carcinoma of the gastrointestinal tract is rare.³ Small cell carcinoma originating in the oesophagus is especially uncommon, accounting for only

Figure 4 Positron emission tomography/CT findings after treatment: (A) wall thickening of the gastro-oesophageal junction and lymph node hypertrophy on the lesser curvature side have disappeared. (B) The enhanced fluorodeoxyglucose accumulation prior to treatment is no longer observed.

1–1.5% of all oesophageal cancers.⁴ The incidence of small cell carcinoma in the stomach is also very low, and that with a gastro-oesophageal junction origin is even more rare.⁵

There is a wide range of opinions on treatment for small cell carcinoma originating in the gastro-intestinal tract, with most regimens consisting of chemotherapy, radiotherapy, surgery and various combinations of these strategies. Despite the lack of a well-established standard of care, many investigators have recommended that small cell carcinoma of the gastro-intestinal tract be treated in a manner similar to that of small cell lung cancer because of the clinicopathological similarities between these tumours.⁶ In Japan, based on the studies reported by Kudoh *et al*⁷ and Noda *et al*,⁸ chemotherapy with CDDP plus irinotecan (CPT-11) has been regarded as the standard first-line treatment of patients with small cell lung cancer. Accordingly, the main chemotherapy other than CDDP plus ETP, used to treat small cell carcinoma of the gastrointestinal tract, is CDDP plus CPT-11. In the present patient, we performed chemotherapy with CDDP plus ETP, which remains as a global standard chemotherapy regimen for treating LD small cell lung carcinoma. The present patient had obstruction to the passage of food at the gastro-oesophageal junction owing to the large size of the primary tumour and was unable to take anything by mouth. To relieve this condition, palliative local radiation therapy was used in combination with chemotherapy.

In a study involving patients with extensive small cell lung carcinoma, no statistically significant differences were found in either the response rate or overall survival between the groups treated with CDDP plus ETP and CBDCA plus ETP.⁹ On the basis of the results of that study, CDDP was changed to CBDCA after the onset of renal toxicity in our patient and chemotherapy was continued until four courses had been given. Despite the change from CDDP to CBDCA, this treatment achieved satisfactory effectiveness, indicating that chemotherapy with CBDCA plus ETP may be an appropriate alternative in patients with impaired renal function. There has been no evidence of recurrence, to date, since the completion of CRT in this patient. In the event of recurrence, the optimal treatment strategy should be determined with reference to therapy used for patients with small cell lung cancer, as neither those used after recurrence nor second-line and subsequent chemotherapy regimens have been well established. Such regimens would include topotecan or amrubicin chloride.¹⁰

Fortunately, CR was achieved with CRT and our patient was able to resume oral intake. As a result, enteral nutrition through an intestinal fistula was no longer needed and the intestinal fistula tube was later removed. No distant metastases were detected and lesion spread was limited. Biopsy samples taken during endoscopy after treatment showed no malignant cells. We concluded that CR had been achieved for the primary tumour and curative surgical resection was considered. The survival benefit of surgical resection performed in patients achieving CR or with LD small cell carcinoma has not been fully defined as yet. Whereas there is evidence that surgical resection of LD small cell carcinoma results in long-term disease-free survival (>5 years),^{11–12} this is still not a

well-established treatment modality. The role of surgery after chemotherapy, with or without radiotherapy, was suggested by several other case reports.¹³ After providing a full explanation of the risk of recurrence, we recommended that the patient undergo radical surgery for possible survival benefit. However, he refused surgery and, in fact, surgeons at our hospital were not entirely confident that surgery would be beneficial. Ultimately, radical resection was not performed and he has been closely followed up in our outpatient clinic.

Our experience with this case indicates chemotherapy with CDDP plus ETP or CBDCA plus ETP combined with radiation therapy to be an appropriate treatment option for small cell carcinoma of the gastro-oesophageal junction. However, the effectiveness of this treatment must be fully investigated in a large number of patients. Further accumulation of cases would facilitate elucidation of the underlying pathological mechanisms and thereby allow the optimal treatment modality for patients with small cell carcinoma to be established.

Learning points

- ▶ Chemo-radiotherapy is effective in some cases with small cell carcinoma of the gastro-oesophageal junction.
- ▶ Chemotherapy regimens for small cell carcinoma originating in the gastrointestinal tract are designed based on those for small cell lung cancer.
- ▶ Although cisplatin (CDDP) plus etoposide (ETP) is a standard chemotherapy regimen for small cell carcinoma, carboplatin plus ETP may be effective in cases in which CDDP is contraindicated owing to renal toxicity.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Lieberman MD, Franceschi D, Marsan B, *et al*. Esophageal carcinoma. The unusual variants. *J Thorac Cardiovasc Surg* 1994;**108**:1138–46.
2. Bosman FT, Carneiro F, Hruban RH, *et al*. WHO classification of tumours of the digestive system (World Health Organization Classification of Tumours), Lyon: IARC Press, 2010.
3. Brenner B, Tang LH, Klimstra DS, *et al*. Small-cell carcinomas of the gastrointestinal tract: a review. *J Clin Oncol* 2004;**22**:2730–9.
4. Law SY, Fok M, Lam KY, *et al*. Small cell carcinoma of the esophagus. *Cancer* 1994;**73**:89–94.
5. Richards D, Davis D, Yan P, *et al*. Unusual case of small cell gastric carcinoma: case report and literature review. *Dig Dis Sci* 2011;**56**:951–7.
6. Brenner B, Tang LH, Shia J, *et al*. Small cell carcinoma of the gastrointestinal tract: clinicopathological features and treatment approach. *Semin Oncol* 2007;**34**:43–50.
7. Kudoh S, Fujiwara Y, Takada Y, *et al*. Phase II study of irinotecan combined with cisplatin in patients with previously untreated small-cell lung cancer. West Japan Lung Cancer Group. *J Clin Oncol* 1998;**16**:1068–74.
8. Noda K, Nishiwaki Y, Kawahara M, *et al*. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;**346**:85–91.
9. Okamoto H, Watanabe K, Kunikane H, *et al*. Randomized phase III trial of carboplatin plus etoposide vs split dose of cisplatin in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. *Br J Cancer* 2007;**97**:162–9.

10. **Asayama M**, Fuse N, Yoshino T, *et al*. Amrubicin for the treatment of neuroendocrine carcinoma of the gastrointestinal tract: a retrospective analysis of five cases. *Cancer Chemother Pharmacol* 2011;**68**:1325–30.
11. **Yachida S**, Matsushita K, Usuki H, *et al*. Long-term survival after resection for small cell carcinoma of the esophagus. *Ann Thorac Surg* 2007;**72**:596–7.
12. **Nishimaki T**, Suzuki T, Nakagawa S, *et al*. Tumor spread and outcome of treatment in primary esophageal small cell carcinoma. *J Surg Oncol* 1997;**64**:130–4.
13. **Muto I**, Nishimaki T, Aizawa K, *et al*. Primary small cell carcinoma of the esophagus: report of a case. *Surg Today* 1995;**25**:830–5.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Matsunaga M, Miwa K, Noguchi T, Sasaki Y. Small cell carcinoma of gastro-oesophageal junction with remarkable response to chemo-radiotherapy. *BMJ Case Reports* 2012;10.1136/bcr-2012-006361, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow