Acta Medica Okayama

Volume 63, *Issue* 5 2009 *Article* 10

OCTOBER 2009

Two cases of primary small cell carcinoma of the stomach

Masaya Iwamuro[*] Shouichi Tanaka[†] Akihiro Bessho[‡]

Hideaki Takahashi[**] Takeyuki Ohta[††]

Rie Takada[‡‡] Ichiro Murakami[§]

[*]Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,

[†]Department of Internal Medicine, National Hospital Organization Iwakuni Clinical Center,

[‡]Department of Internal Medicine, National Hospital Organization Iwakuni Clinical Center,

[**]Department of Internal Medicine, National Hospital Organization Iwakuni Clinical Center,

[††]Department of Internal Medicine, National Hospital Organization Iwakuni Clinical Center,

[‡‡]Department of Pathology, National Hospital Organization Iwakuni Clinical Center,

[§]Department of Pathology, National Hospital Organization Iwakuni Clinical Center,

Two cases of primary small cell carcinoma of the stomach

Masaya Iwamuro, Shouichi Tanaka, Akihiro Bessho, Hideaki Takahashi, Takeyuki Ohta, Rie Takada, and Ichiro Murakami

Abstract

We report 2 cases of small cell carcinoma (SmCC) of the stomach with distant metastasis that were treated with the same chemotherapeutic regimens as used to treat small cell lung cancer. Although the mean survival of patients with SmCC of the stomach is reported to be only 7 months, our patients survived for 15 and 14 months, respectively. In our experience, these chemotherapeutic regimens might provide a survival benefit for patients with SmCC of the stomach, although they demonstrated no remarkable antitumor effects.

KEYWORDS: small cell carcinoma, extrapulmonary small cell carcinoma, neuroendocrine cell carcinoma, gastric cancer

Acta Med. Okayama, 2009
Vol. 63, No. 5, pp. 293–298

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

Two Cases of Primary Small Cell Carcinoma of the Stomach

Masaya Iwamuro[a,b]*, Shouichi Tanaka[b], Akihiro Bessho[b], Hideaki Takahashi[b], Takeyuki Ohta[b], Rie Takada[c], and Ichiro Murakami[c]

[a]Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan,
Departments of [b]Internal Medicine, and [c]Pathology, National Hospital Organization Iwakuni Clinical Center, Iwakuni, Yamaguchi 740–8510, Japan

We report 2 cases of small cell carcinoma (SmCC) of the stomach with distant metastasis that were treated with the same chemotherapeutic regimens as used to treat small cell lung cancer. Although the mean survival of patients with SmCC of the stomach is reported to be only 7 months, our patients survived for 15 and 14 months, respectively. In our experience, these chemotherapeutic regimens might provide a survival benefit for patients with SmCC of the stomach, although they demonstrated no remarkable antitumor effects.

Key words: small cell carcinoma, extrapulmonary small cell carcinoma, neuroendocrine cell carcinoma, gastric cancer

Primary small cell carcinoma (SmCC) of the stomach, synonymous with neuroendocrine carcinoma of the stomach, is a rare neoplasm that represents less than 0.1% of all primary gastric cancers [1–4]. This neoplasm is one of the most aggressive cancers, and has a very poor prognosis [5]. In fact, the mean survival of patients with primary SmCC of the stomach is reported to be 7 months [6].

The choice of treatment for this disease remains controversial. The therapeutic value of surgery, systemic chemotherapy, and locoregional chemotherapy is often limited. Some authors have suggested that the chemotherapy regimens for small cell lung cancer (SCLC) may be suitable for patients with this disease due to the similarity in biological and clinical characteristics between SmCC of the stomach and SCLC [5, 7, 8]. We report herein 2 cases with advanced primary SmCC of the stomach who were treated with the same chemotherapy regimens as used to treat SCLC. The resulting survival times for these 2 patients were over 15 and 14 months, respectively.

Received December 9, 2008; accepted May 7, 2009.
*Corresponding author. Phone: +81–86–235–7219; Fax: +81–86–225–5991
E-mail: iwamuro@mc.neweb.ne.jp (M. Iwamuro)

Case Report

Case 1. A 79-year-old Japanese woman had been undergoing treatment for liver cirrhosis due to hepatitis C virus infection for several years. A periodic computed tomography (CT) scan incidentally revealed an enlarged lymph node around the lesser curvature of the stomach and a hypoattenuated lesion in the spleen (Fig. 1). The patient was asymptomatic, and her physical examinations were unremarkable. Laboratory studies revealed a low white blood cell count of 2,900/mm^3 and a low platelet count of 53,000/mm^3, due to the hypersplenism. Liver function tests showed a normal bilirubin level, and slightly

elevated transaminase levels. Tumor markers including carcinoembryonic antigen (CEA), carbohydrate antigen 19–9, alphafetoprotein, des-gamma-carboxy prothrombin, neuron-specific enolase (NSE), and progastrin-releasing peptide were all within normal limits.

Esophagogastroduodenoscopy (EGD) disclosed a gastric cancer of Borrman type 2 with a diameter of 25 mm (Fig. 2). Pathologic examination of the biopsy specimens revealed small or medium-sized cancer cells with irregular nuclei and scant cytoplasm (Fig. 3). The tumor cells were weakly positive for immunohistochemical staining with chromogranin. Based on the histological findings, the diagnosis of SmCC was confirmed. No adenocarcinoma component was detected in the biopsy specimens. Neither the swollen lymph node

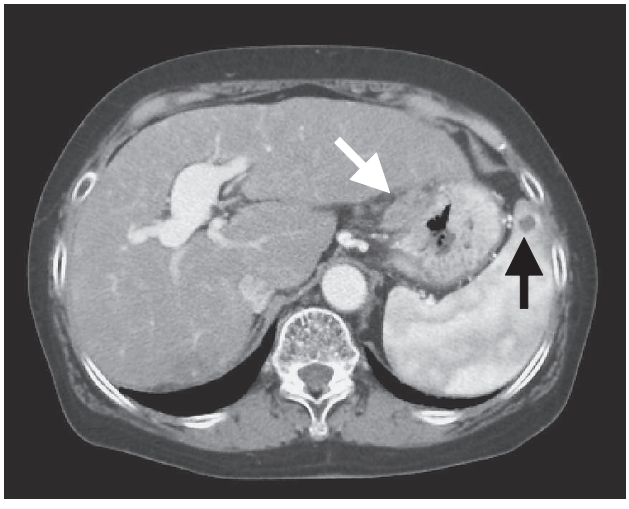

Fig. 1 Contrast-enhanced computed tomography scan of case 1. An enlarged lymph node 20 mm in diameter was demonstrated around the lesser curvature of the stomach (white arrow). A hypoattenuated lesion 10 mm in diameter was also revealed in the spleen, which was considered to be a metastasis of small cell carcinoma of the stomach (black arrow).

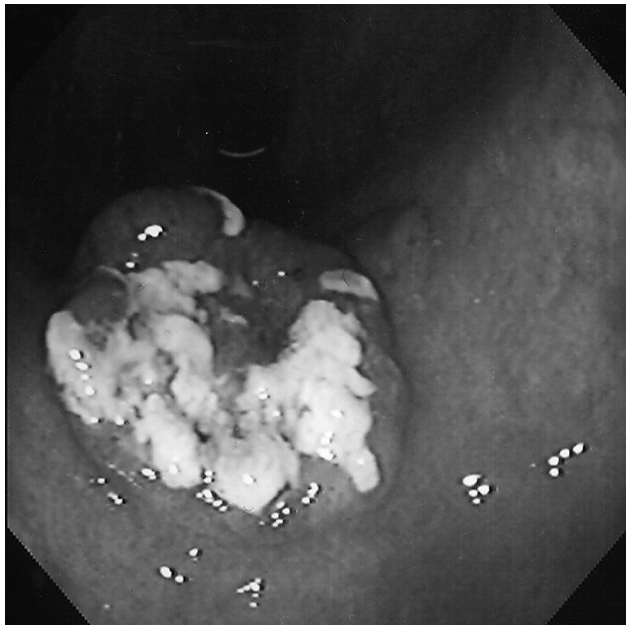

Fig. 2 Esophagogastroduodenoscopic image from case 1. A tumor of Borrman type 2 in the lesser curvature of the gastric body can be observed.

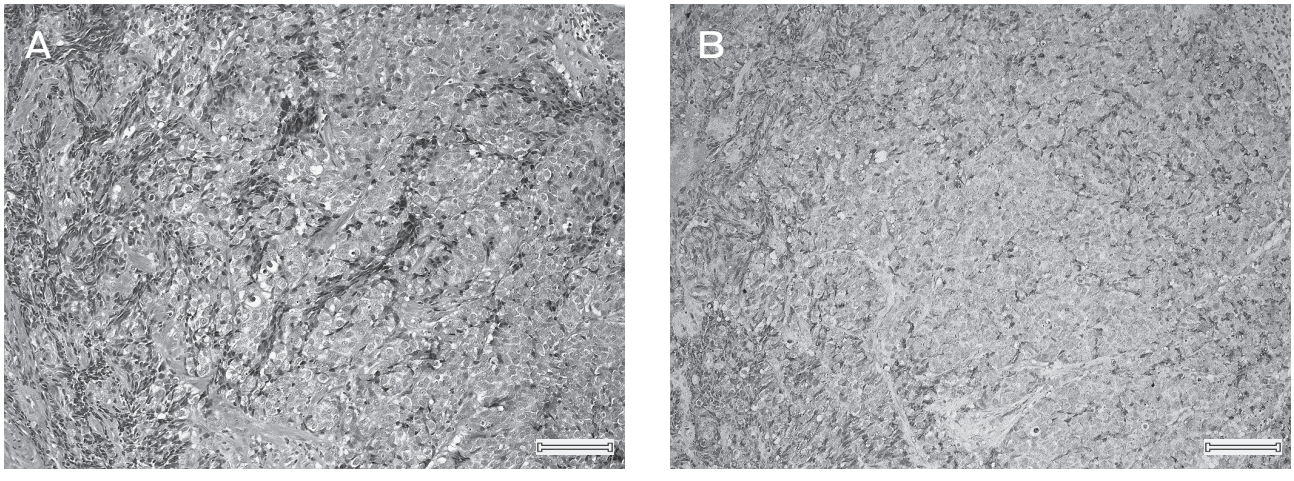

Fig. 3 Histological appearance of the small cell carcinoma of the stomach in case 1. Biopsy specimens revealed small or medium-sized cancer cells with irregular nuclei and scant cytoplasm (A); hematoxylin and eosin staining. The tumor cells were weakly positive for chromogranin (B); immunohistochemical staining with chromogranin. Scale bars = 200 μm.

around the stomach nor the hypoattenuated lesion in the spleen had been detected by CT over the previous year, so both findings were considered to be metastases of SmCC. Contrast-enhanced CT of the whole body revealed no tumor in the lung or other organs. The clinical diagnosis based on these findings was primary SmCC of the stomach, T2 N1 H0 P0 CYx M1: c Stage IV, according to the Japanese Classification of Gastric Carcinoma (9).

The doses of the chemotherapeutic agents were reduced due to the low platelet count. The first line of chemotherapy consisted of i.v. carboplatin (AUC = 4) on Day 1, plus i.v. etoposide at a dose of 50 mg/m^2 daily for 3 days on Days 1–3, every 4 weeks (Fig. 4). The patient's condition remained stable during four cycles of the chemotherapy, but after 5 cycles, paraaortic lymphadenopathy newly appeared, while the size of the primary gastric tumor had not changed. The second line of chemotherapy consisted of i.v. nogitecan hydrochloride at a dose of 0.8 mg/m^2 daily for 5 days on Days 1–5, every 3 weeks. Both the primary gastric lesion and lymphadenopathy were enlarged after 2 cycles of the chemotherapy, so the presence of progressive disease was acknowledged. The third line of chemotherapy was i.v. amrubicin hydrochloride 35 mg/m^2 daily for 3 days on Days 1–3, but this regimen was stopped after one cycle due to the hematologic toxicity. The fourth line of chemotherapy consisted of i.v. paclitaxel at a dose of 45 mg/m^2 daily for 2 days on Days 1 and 8, every 3 or 4 weeks. After 3 cycles of the chemotherapy, disease progression was still observed. The fifth line of chemotherapy was i.v. gemcitabine hydrochloride at a dose of 500 mg/m^2 for 2 days on Days 1 and 8. A new metastatic lesion appeared on the skin of the patient's right forearm during the course of therapy. Her condition continued to worsen and died 15 months after the diagnosis of SmCC of the stomach.

Case 2. A 78-year-old Japanese male presented with a backache in the middle of his back that had begun 2 weeks earlier. The patient had neither a relevant history nor a contributory family history. His physical examinations were unremarkable. Laboratory studies revealed a normal complete blood count and normal levels of liver enzymes. NSE was elevated to 23.66 ng/ml (normal 0–15.2). The other tumor markers were all within the normal limits. An ultrasound examination revealed 3 tumors in the liver, and these liver tumors were identified as low-density masses in a contrast-enhanced CT scan. There was no tumor in the lungs or lymphadenopathy on CT scans. EGD disclosed a gastric cancer of Borrman type 2 with a diameter of 35 mm in the posterior wall of the gastric body (Fig. 5). Pathological examination of the biopsy specimen confirmed the diagnosis of SmCC (Fig. 6). A bone scintigraphy exam showed multiple metastatic lesions in the thoracic spine, the right sacrum, and the right ischium. The clinical diagnosis based on these findings was primary SmCC of the stomach with metastases to the bone and the liver, T2 N0 H1 P0 CYx M1: c Stage IV.

Opioids and non-steroidal anti-inflammatory drugs were administered for the patient's backache due to the bone metastasis, and a total of 40 Gy of radiotherapy was administered to the thoracic spine (Fig. 7). The backache was temporarily alleviated by the radiotherapy and the analgesics. The first line of chemotherapy consisted of i.v. carboplatin (AUC = 5) on Day 1, plus i.v. etoposide at a dose of 70 mg/m^2 daily for 3 days on Days 1–3, every 4 weeks. Both the primary gastric lesion and the hepatic tumors were enlarged after two cycles of the chemotherapy. The

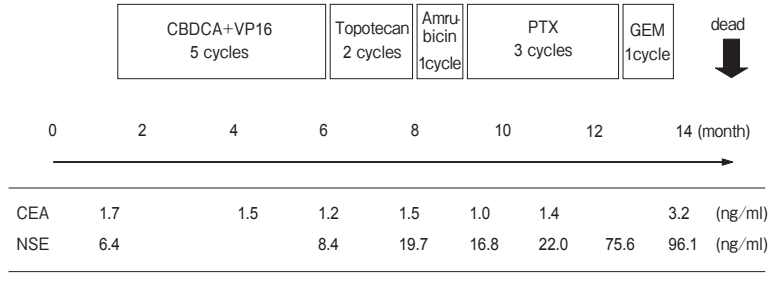

Fig. 4 Clinical course of case 1. CBDCA, carboplatin; VP16, etoposide; PTX, paclitaxel; GEM, gemcitabine hydrochloride; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase.

second and third lines of chemotherapy consisted of 0.8 mg/m^2 nogitecan hydrochloride and 35 mg/m^2 amrubicin hydrochloride, respectively. However, no remarkable responses were achieved with those regimens. Thereafter, the patient rapidly deteriorated and died 15 months after the diagnosis.

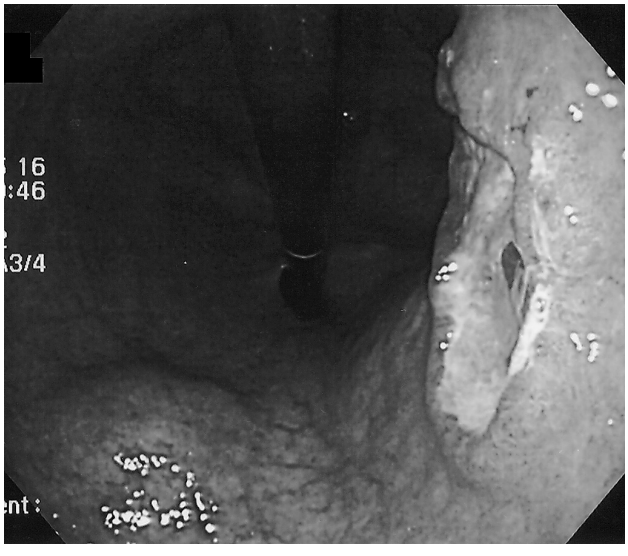

Fig. 5 Esophagogastroduodenoscopic image in case 2. A cancer of Borrman type 2 in the posterior wall of the gastric body was revealed.

Discussion

The vast majority of SmCC develop in the lung, with only 2.5% of SmCC present at extrapulmonary sites [10, 11], including the stomach, esophagus, colon, pancreas, minor salivary organs, pharynx, and uterine cervix. The morphological features of extrapulmonary SmCC are identical to those of SCLC [12].

To the best of our knowledge, 213 cases of primary SmCC of the stomach have been reported in the literature (168 males, 44 females, 1 unspecified). The patients ranged in age from 28 to 89 years, with a mean of 65.1 years, at initial diagnosis. The gross type was type 0-I in 2, 0-IIa in 2, 0-IIa + IIc in 3, 0-IIb in 1, 0-IIb + Ia in 1, 0-IIc in 3, 0-IIc + IIa in 4, 0-III + IIc in 1, type 1 in 30, type 2 in 67, type 3 in 46, type 4 in 3, and type 5 in 8 cases (unspecified in 42 cases), according to the Japanese Classification of Gastric Carcinoma (9). The tumor sizes ranged in diameter from 8 to 185 mm, with a mean of 58.7 mm. The tumor was limited to the mucosa or submucosa in only 15 cases, whereas 112 cases presented with advanced-stage disease. The overall median survival time (MST) was only 9 months (range: 0-96 months). In general, the clinical behavior of primary SmCC of the stomach is generally aggressive, similar to that of SCLC [13]. Nodal involvement and distant metastases are frequently observed at the initial presentation [14, 15]. Because of its clinicopathological aggres-

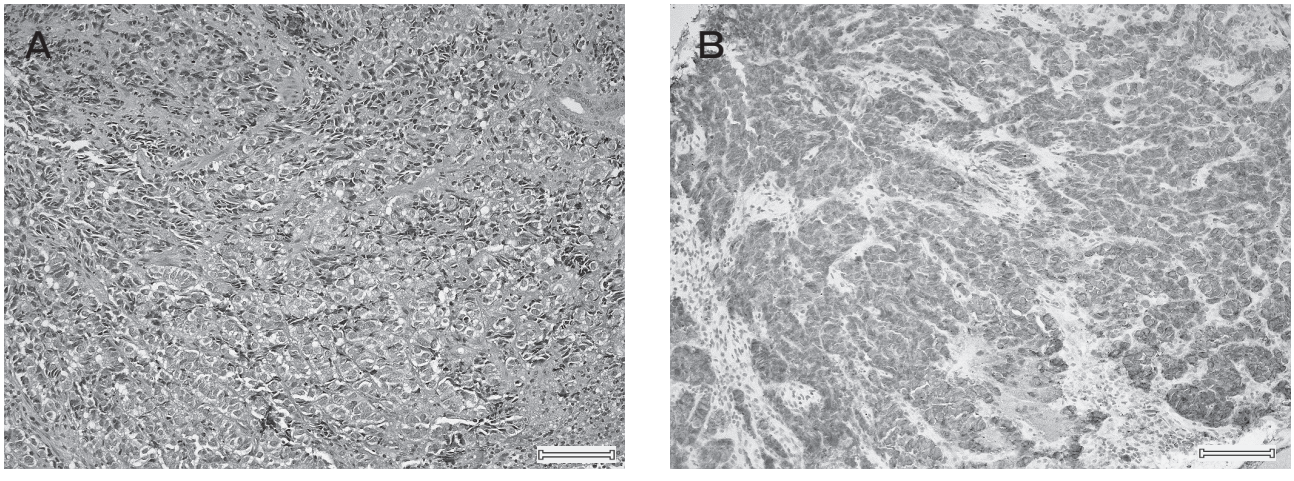

Fig. 6 Histological appearance of the small cell carcinoma of the stomach in case 2. Cancer cells with irregular nuclei and scant cytoplasm were arranged in a trabecular pattern (A); hematoxylin and eosin staining. The cancer cells were positive for synaptophysin (B); immunohistochemical staining with synaptophysin. Scale bars: 200 μm.

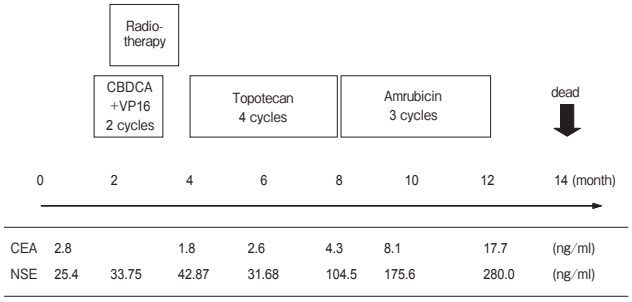

Fig. 7 Clinical course of case 2.

siveness, this disease is considered to have a poor prognosis [6]. Although a standard treatment has not yet been established for primary SmCC of the stomach, surgery may play an important role in cases without distant metastasis. Of the cases reported in the literature, surgery without adjuvant chemotherapy was performed in 77 cases and the MST was 20 months. Alternatively, 47 patients underwent various regimens of chemotherapy as adjuvant therapy after surgery. Among these, 15 received etoposide-based or irinotecan-based chemotherapy and the MST was 15 months. 5-fluorouracyl (5-FU)-based chemotherapy was applied for 21 patients, uracyl/tegafur (UFT)-based chemotherapy for 11, and tegafur/gimeracil/oteracil potassium (S-1)-based chemotherapy for 16, and the MST was 17, 12, and over 20 months, respectively.

In contrast, 17 cases of primary SmCC of the stomach treated by monotherapy with cytotoxic agents have been reported. Although various regimens of chemotherapy were administered to these patients, only 3 of the 17 cases survived over 12 months after the initial diagnosis [16–18]. Carboplatin and etoposide were administered in one patient who survived for only 7 months [19], and cisplatin and etoposide were administered in 2 patients who survived for 9 and 11 months, respectively [20, 21]. None of these 3 cases underwent salvage regimens. Both of the present patients survived over 12 months with carboplatin and etoposide together with salvage regimens that are usually applied to patients with SCLC. Thus, these chemotherapeutic regimens might improve the prognosis of patients with SmCC of the stomach with distant metastasis.

Among elderly Japanese patients with SCLC, chemotherapy with carboplatin and etoposide has achieved a response rate of 75% and a median survival time of 10.8 months, with less toxicity than treatment by cisplatin and etoposide [22]. This regimen seems to have similar effects on primary SmCC of the stomach, possibly because of the biological resemblance between SmCC and SCLC [23]. Single-agent topotecan is one of the most frequently used drugs in the second-line regimen for patients with SCLC. Topotecan has yielded response rates of approximately 20%, with median survival times of approximately 6.3 months [24]. Amrubicin [25], paclitaxel [26], and gemcitabine [27] have also exhibited significant activity against relapsed SCLC. We therefore administered carboplatin and etoposide, single-agent topotecan, amrubicin, paclitaxel, and gemcitabine hydrochloride as the first-, second-, third-, fourth-, and fifth-line regimens for the present patients, respectively. However, although the present patients with distant metastases survived for 15 and 14 months, no remarkable response against the tumor was achieved. It should be investigated in the future whether chemotherapy regimens showing some success against SCLC can prevent the tumor progression of SmCC of the stomach and thus provide a survival benefit for these patients.

On the other hand, S-1, which contains a prodrug of 5-FU, has been widely used as the main drug to treat gastric adenocarcinomas in Japan. In a previous report of a case of primary SmCC of the stomach treated by chemotherapy with S-1 and cisplatin, the patient survived for 14 months [16]. In addition, as described above, S-1 has been shown to have a superior effect as an adjuvant chemotherapeutic drug for gastric SmCC compared with other agents. Thus S-1 is another candidate key drug that could possibly improve the prognosis of patients with SmCC of the stomach [14].

In conclusion, our 2 patients with SmCC of the stomach underwent chemotherapeutic regimens with carboplatin and etoposide, and the salvage regimens that are usually applied to SCLC. With this treatment, they survived for 15 and 14 months despite distant metastases. However, the treatment regimens appeared to have no significant antitumor effects. Comparative analysis between these regimens and S-1-based regimens should be performed in the future.

References

1. Kusayanagi S, Konishi K, Miyasaka N, Sasaki K, Kurahashi T, Kaneko K, Akita Y, Yoshikawa N, Kusano M, Yamochi T, Kushima M and Mitamura K: Primary small cell carcinoma of the stomach. J Gastroenterol Hepatol (2003) 18: 743–747.
2. Hiroshima K, Iyoda A, Shida T, Shibuya K, Iizasa T, Kishi H, Tanizawa T, Fujisawa T and Nakatani Y: Distinction of pulmonary large cell neuroendocrine carcinoma from small cell lung carcinoma: a morphological, immunohistochemical, and molecular analysis. Mod Pathol (2006) 19: 1358–1368.
3. Matsusaka T, Watanabe H and Enjoji M: Oat-cell carcinoma of the stomach. Fukuoka Igaku Zasshi (1976) 67: 65–73.
4. Matsui K, Jin XM, Kitagawa M and Miwa A: Clinicopathologic features of neuroendocrine carcinomas of the stomach: appraisal of small cell and large cell variants. Arch Pathol Lab Med (1998) 122: 1010–1017.
5. Cioppa T, Marrelli D, Neri A, Caruso S, Pedrazzani C, Malagnino V, Pinto E and Roviello F: A case of small-cell gastric carcinoma with an adenocarcinoma component and hepatic metastases: treatment with systemic and intra-hepatic chemotherapy. Eur J Cancer Care (Engl) (2007) 16: 453–457.
6. Matsui K, Kitagawa M, Miwa A, Kuroda Y and Tsuji M: Small cell carcinoma of the stomach: a clinicopathologic study of 17 cases. Am J Gastroenterol (1991) 86: 1167–1175.
7. Arai K and Matsuda M: Gastric small-cell carcinoma in Japan: a case report and review of the literature. Am J Clin Oncol (1998) 21: 458–461.
8. Takaku H, Oka K, Naoi Y, Santoh N, Setsu Y and Mori N: Primary advanced gastric small cell carcinoma: a case report and review of the literature. Am J Gastroenterol (1999) 94: 1402–1404.
9. Japanese Gastric Cancer Association: Japanese classification of gastric carcinoma - 2nd English edition -. Gastric Cancer (1998) 1: 10–24.
10. Remick SC, Hafez GR and Carbone PP: Extrapulmonary small-cell carcinoma. A review of the literature with emphasis on therapy and outcome. Medicine (Baltimore) (1987) 66: 457–471.
11. van der Heijden HF and Heijdra YF: Extrapulmonary small cell carcinoma. South Med J (2005) 98: 345–349.
12. Simon R, Bourne PA, Yang Q, Spaulding BO, di Sant'Agnese PA, Wang HL and Xu H: Extrapulmonary small cell carcinomas express K homology domain containing protein overexpressed in cancer, but carcinoid tumors do not. Hum Pathol (2007) 38: 1178–1183.
13. Vrouvas J and Ash DV: Extrapulmonary small cell cancer. Clin Oncol (R Coll Radiol) (1995) 7: 377–381.
14. Koide N, Suzuki A, Saito H, Sato T, Murakami M, Ota H and Miyagawa S: Gastric small cell carcinoma successfully treated by surgery and postoperative chemotherapy consisting of cisplatin and S-1: report of a case. Surg Today (2007) 37: 989–994.
15. Namikawa T, Kobayashi M, Okabayashi T, Ozaki S, Nakamura S, Yamashita K, Ueta H, Miyazaki J, Tamura S, Ohtsuki Y and Araki K: Primary gastric small cell carcinoma: report of a case and review of the literature. Med Mol Morphol (2005) 38: 256–261.
16. Shimada M, Iwase H, Iyo T, Nakarai K, Kaida S, Indo T, Doi R, Okeya M and Goto H: A case of complete response in a primary lesion treated by combined chemotherapy of TS-1 and CDDP for small cell carcinoma of the stomach with liver metastasis. Gan to kagaku ryoho (Jpn J Cancer Chemotherpy) (2004) 31: 593–596 (in Japanese).
17. Akasofu M, Kawahara E, Nemoto T, Nonomura A and Nakanishi I: An autopsy case of gastric small cell carcinoma in which the tumor completely disappeared with chemotherapy. Gan no rinsho (Jpn J Cancer Clin) (1999) 45: 143–149 (in Japanese).
18. O'Byrne KJ, Cherukuri AK, Khan MI, Farrell RJ, Daly PA, Sweeney EC and Keeling PW: Extrapulmonary small cell gastric carcinoma. A case report and review of the literature. Acta Oncol (1997) 36: 78–80.
19. Inoue F, Nishida O, Mizumoto T, Furukawa H and Saiga T: Small cell carcinoma of the stomach, report of a case. I to cho (Stomach and Intestine) (1996) 31: 797–801 (in Japanese).
20. Kim JH, Lee SH, Park J, Kim HY, Lee SI, Nam EM, Park JO, Kim K, Jung CW, Im YH, Kang WK, Lee MH and Park K: Extrapulmonary small-cell carcinoma: a single-institution experience. Jpn J Clin Oncol (2004) 34: 250–254.
21. van der Gaast A, Verwey J, Prins E and Splinter TAW: Chemotherapy as treatment of choice in extrapulmonary undifferentiated small cell carcinoma. Cancer (1990) 65: 422–424.
22. Okamoto H, Watanabe K, Nishiwaki Y, Mori K, Kurita Y, Hayashi I, Masutani M, Nakata K, Tsuchiya S, Isobe H and Saijo N: Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. J Clin Oncol (1999) 17: 3540–3545.
23. Lo Re G, Canzonieri V, Veronesi A, Dal Bo V, Barzan L, Zancanaro C and Trovo M: Extrapulmonary small cell carcinoma: a single-institution experience and review of the literature. Ann Oncol (1994) 5: 909–913.
24. von Pawel J, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, Stewart DJ, Clark PI, Palmer MC, Depierre A, Carmichael J, Krebs JB, Ross G, Lane SR and Gralla R: Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol (1999) 17: 658–667.
25. Onoda S, Masuda N, Seto T, Eguchi K, Takiguchi Y, Isobe H, Okamoto H, Ogura T, Yokoyama A, Seki N, Asaka-Amano Y, Harada M, Tagawa A, Kunikane H, Yokoba M, Uematsu K, Kuriyama T, Kuroiwa Y and Watanabe K: Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer: Thoracic Oncology Research Group Study 0301. J Clin Oncol (2006) 24: 5448–5453.
26. Smit EF, Fokkema E, Biesma B, Groen HJ, Snoek W and Postmus PE: A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer (1998) 77: 347–351.
27. Masters GA, Declerck L, Blanke C, Sandler A, DeVore R, Miller K and Johnson D; Eastern Cooperative Oncology Group: Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol (2003) 21: 1550–1555.