JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(4)313–318
doi:10.1093/jjco/hyp173
Advance Access Publication 4 January 2010

Cisplatin and Etoposide as First-line Chemotherapy for Poorly Differentiated Neuroendocrine Carcinoma of the Hepatobiliary Tract and Pancreas

Satoru Iwasa[1], Chigusa Morizane[1*], Takuji Okusaka[1], Hideki Ueno[1], Masafumi Ikeda[2], Shunsuke Kondo[1], Tsutomu Tanaka[1,3], Kohei Nakachi[2], Shuichi Mitsunaga[2], Yasushi Kojima[2], Atsushi Hagihara[1] and Nobuyoshi Hiraoka[4]

[1]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, Tokyo, [2]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital East, Chiba, [3]Department of Gastroenterology, Nagoya University Graduate School of Medicine, Nagoya and [4]Pathology Division, National Cancer Center Research Institute, Tokyo, Japan

*For reprints and all correspondence: Chigusa Morizane, Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: cmorizan@ncc.go.jp

Received October 8, 2009; accepted November 4, 2009

Objective: The combination chemotherapy consisting of cisplatin and etoposide, one of the standard regimens for small cell lung cancer, has been widely used to treat extrapulmonary poorly differentiated neuroendocrine carcinomas. However, there were no prior reports limited to the hepatobiliary tract and pancreas as the primary sites.
Methods: We reviewed the cases in our database from October 1995 to January 2009 and retrospectively examined the clinical data of patients, with unresectable or recurrent poorly differentiated neuroendocrine carcinoma arising from the hepatobiliary tract and pancreas, who received combination chemotherapy with cisplatin and etoposide as the first-line treatment. The chemotherapy regimen consisted of cisplatin 80 mg/m^2 given intravenously on day 1 and etoposide 100 mg/m^2 intravenously on days 1–3, repeated every 3–4 weeks.
Results: Twenty-one patients were treated with the above regimen of cisplatin and etoposide combination chemotherapy. The primary tumor site was the liver in 2 patients, gallbladder in 8 patients, pancreas in 10 patients and ampulla of Vater in 1 patient. Although no complete responses were obtained, three patients had partial responses, resulting in an overall response rate of 14%. Median progression-free survival was 1.8 months, and median overall survival was 5.8 months. The major adverse events were myelosuppression and gastrointestinal toxicities, with Grade 3 or 4 neutropenia (90%), nausea (33%) and anorexia (24%).
Conclusions: Cisplatin and etoposide combination as the first-line chemotherapy for hepatobiliary or pancreatic poorly differentiated neuroendocrine carcinoma had only marginal antitumor activity and relatively severe toxicity compared with previous studies on extrapulmonary poorly differentiated neuroendocrine carcinoma treated with the same regimen.

Key words: cisplatin – etoposide – neuroendocrine carcinoma – chemotherapy

INTRODUCTION

Neuroendocrine tumors are rare tumors that exhibit a variety of morphologic, functional and behavioral characteristics (1). The aggressiveness of these tumors varies greatly depending on the histological degree of differentiation, from well-differentiated neuroendocrine tumors to poorly differentiated neuroendocrine carcinomas (PD-NECs).

No standard treatment for unresectable extrapulmonary PD-NECs has been established yet. However, combined chemotherapy with cisplatin and etoposide, one of the standard regimens employed for the treatment of small cell lung cancer (SCLC), has been used widely for the treatment of extrapulmonary PD-NECs, because the genetic, pathological and clinical features of PD-NECs overlap with those of SCLC (2–6). The previous reports, in general, refer to a

wide variety of extrapulmonary sites of origin of the primary tumors, partly because the rarity of the disease precludes clinical studies devoted to each individual primary origin of the tumors. Thus, there have been no prior reports of treatment limited to neuroendocrine tumors arising from the hepatobiliary and pancreatic region as primary sites.

It is well established that adenocarcinomas arising from the hepatobiliary tract or pancreas have a worse prognosis when compared with that of gastric or colorectal adenocarcinomas, despite the histologies being similar. It remains to be determined whether these tumors of different primary origins can be included within the same group for treatment.

Therefore, it has not yet been clarified whether combined chemotherapy with cisplatin and etoposide might be as effective against hepatobiliary and pancreatic PD-NECs as it is for miscellaneous extrapulmonary PD-NECs. We report our experience of combined chemotherapy with cisplatin and etoposide as the first-line chemotherapy for patients with unresectable or recurrent PD-NECs, focusing on the tumors arising from the hepatobiliary tract and pancreas.

PATIENTS AND METHODS

Patients

Between October 1995 and January 2009, in total, 25 patients with PD-NEC arising from the hepatobiliary tract and pancreas were treated at the National Cancer Center Hospital, Tokyo, Japan. Of these 25 patients, 21 received the combination of cisplatin and etoposide as the first-line chemotherapy. Before the chemotherapy, tumor specimen obtained by a fine-needle biopsy or a surgical resection was pathologically diagnosed as PD-NECs according to the WHO classification (7,8). Typically, tumor tissue showed a dense proliferation of round or polygonal tumor cells with hyperchromatic nuclei and pale to eosinophilic granular cytoplasm, arranged in sheets, nests and cords. Extensive necrosis and mitotic figures were frequently observed. Immunohistochemically, the tumor cells expressed endocrine markers, such as chromogranin A, synaptophysin, neuron-specific enolase (NSE) and/or CD56. A Ki-67 proliferation index $>15\%$ was documented in the 21 patients receiving the cisplatin plus etoposide combination chemotherapy.

Treatment Schedule

Cisplatin, 80 mg/m^2, was administered intravenously (IV) over 2 h on the first day with adequate hydration. Etoposide, 100 mg/m^2/day, was administered IV over 2 h on days 1–3. This treatment was repeated every 3–4 weeks for a maximum of six cycles unless disease progression or unacceptable toxicity occurred. In two patients, a modified schedule with split-dose administration of cisplatin at a dose of 25 mg/m^2/day IV on days 1–3 and a reduced dose of etoposide 80 mg/m^2/day IV on days 1–3 was selected from the first cycle because of advanced age and poor performance status (9).

Antiemetic prophylaxis with 5-HT3 antagonists plus dexamethasone was used at the physician's discretion. Recombinant human granulocyte colony-stimulating factor was administered if patients developed febrile neutropenia.

Response and Toxicity Evaluations

Tumor assessments by computed tomographic (CT) scan of the abdomen were carried out at baseline and every cycle according to the Response Evaluation Criteria in Solid Tumors (RECIST). CT scan of the chest was carried out at the baseline and every cycle if a chest X-ray as a screening test detected lung metastases. Responses were to be confirmed by repeated assessments carried out no less than 4 weeks apart. In addition, tumor markers of carcinoembryonic antigen (CEA), cancer antigen (CA)19-9, NSE and progastrin-releasing peptide (ProGRP) were measured every cycle. All adverse events were reviewed based on medical records and evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical Analysis

Overall survival was measured from the date of initial treatment to the date of death or the date of the last follow-up. Death from any cause was considered an event. Survival curves were constructed using the Kaplan–Meier method. Statistical analyses were performed using Dr. SPSS II (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Characteristics

The characteristics of the 21 treated patients are listed in Table 1. The median age of the patients was 57 years, with an almost equal gender distribution. One patient (5%) had metastatic recurrent disease after surgery with curative intent, and 20 (95%) had unresectable metastatic disease at the initial diagnosis. Of the 21 patients, 20 (95%) had elevated serum NSE level and 4 (19%) had elevated serum ProGRP level. The primary tumor sites included the pancreas in 10 patients (48%), gallbladder in 8 (38%), liver in 2 (10%) and ampulla of Vater in 1 (5%). Two patients with multiple liver tumors without a definite primary site were classified as having a liver origin. The most common metastatic site was the liver. Other common sites were lymph nodes and the peritoneum.

Treatment

In total, 57 cycles were administered to the 21 patients with a median of 2 cycles per patient (range, 1–6 cycles). Eight

Table 1. Patient characteristics ($n = 21$)

Characteristics	*n* (%)
Age (years)	
Median	57
Range	30–70
Sex	
Male	11 (52)
Female	10 (48)
ECOG performance status	
0	9 (43)
1	10 (48)
2	2 (10)
Primary tumor site	
Liver	2 (10)
Gallbladder	8 (38)
Pancreas	10 (48)
Ampulla of Vater	1 (5)
Metastatic site	
Liver	17 (81)
Lung	2 (10)
Spleen	1 (5)
Bone	1 (5)
Adrenal gland	1 (5)
Pleural	1 (5)
Lymph node	11 (52)
Peritoneum/ascites	11 (52)
CEA	
Abnormal	13 (62)
Normal	8 (38)
CA19-9	
Normal	13 (62)
Abnormal	8 (38)
NSE (ng/ml)	
Median	143.1
Range	6–1930
ProGRP[a] (U/ml)	
Median	25.5
Range	11.9–63 090

Abnormal carcinoembryonic antigen (CEA) and CA19-9 represented $\geq$5 ng/ml and $\geq$37 U/ml, respectively. ECOG, Eastern Cooperative Oncology Group; NSE, neuron-specific enolase; ProGRP, pro-gastrin-releasing peptide.
[a]One patient did not have pre-treatment data examination.

patients (38%) required dose reductions during therapy. Of these patients, three required 20–25% dose reductions for both cisplatin and etoposide due to febrile neutropenia and renal dysfunction, three required a 20% dose reduction of etoposide alone due to febrile neutropenia and the remaining two required a 20% dose reduction of cisplatin alone due to serum creatinine level elevation. The median relative intensities of the doses of cisplatin and etoposide (calculated as the actual dose delivered divided by the intended dose of 3-week interval regimen) were 79% and 73%, respectively. The reasons for treatment discontinuation were radiological progressive disease in 15 patients, clinical progressive disease in 1 patient, unacceptable toxicities in 2 (gastrointestinal toxicity of prolonged Grade 2 nausea and anorexia in one, and renal toxicity as indicated by decreased creatinine clearance to $<$35 ml/min in the other), cytoreductive surgery in 1 and refusal of treatment by 1 (mental suffering). As for the patient who underwent cytoreductive surgery, she could not maintain response duration until the next course. In addition, she had multiple liver metastases with the maximum size of $>$13 cm produced abdominal discomfort.

After treatment discontinuation, eight patients received second-line chemotherapy: gemcitabine monotherapy was administered to four patients, irinotecan monotherapy to three, and combination chemotherapy with cisplatin, vincristine, doxorubicin and etoposide (CODE therapy) to one. Among them, one patient, who developed disease progression after one cycle of cisplatin and etoposide, achieved a partial response after two cycles of second-line chemotherapy with gemcitabine. Three patients were treated employing other therapeutic modalities, i.e. cytoreduction surgery, allogeneic peripheral blood stem cell transplantation and chemoembolization for liver metastases. The remaining nine patients received only supportive care.

Efficacy

At the time of analysis, 2 patients were alive with disease and 19 had died of their disease. All patients were assessable for tumor response. Although no patient achieved a complete response, two with gallbladder and one with pancreatic PD-NECs achieved a partial response, giving an overall response rate of 14% (95% confidence interval, 3–36%). Ten patients (48%) had shown stable disease and the remaining eight (38%) had progressive disease. The duration of the three objective responses were 2.4, 3.1 and 3.5 months. During treatment, the serum NSE level was reduced by $>$50% in 15 (75%) of 20 patients who had shown a pre-treatment level of $\geq$15 ng/ml. All patients were included in the survival assessment. Median progression-free survival, median overall survival and the 1-year survival rate were 1.8, 5.8 months and 5%, respectively (Fig. 1). Median progression-free survival and overall survival in the pancreas group ($n = 10$) were 1.5 and 6.2 months, whereas those in the hepatobiliary tract group ($n = 11$) were 3.0 and 5.8 months, although the differences between both groups did not appear to be statistically significant.

Adverse Events

All 21 patients were assessed for toxicities, as listed in Table 2. The most common toxicities were leukopenia and

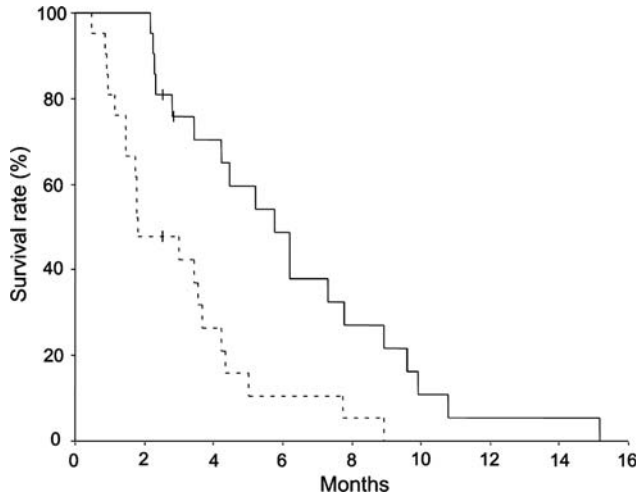

Figure 1. Overall survival (continuous line) and progression-free survival (dotted line) in the 21 patients.

neutropenia. Grade 3 or 4 leukopenia and neutropenia occurred in 15 (71%) and 19 (90%) patients, respectively, and febrile neutropenia in 8 (38%). As to non-hematological toxicities, vomiting of all grades was seen in 81% of the patients, whereas Grade 3 nausea and anorexia occurred in 33% and 24%, respectively. Although these gastrointestinal toxicities were frequently observed after cisplatin administration, most were manageable with appropriate medical treatment and only one patient needed to discontinue therapy due to gastrointestinal toxicity of prolonged Grade 2 nausea and anorexia. No other unexpected severe toxicities were observed during the treatment and there were no treatment-related deaths.

Table 2. Adverse events

	Grade				Grade 3/4, *n* (%)
	1	2	3	4	
Hematological toxicity					
Leukopenia	1	5	7	8	15 (71)
Neutropenia	1	1	2	17	19 (90)
Anemia	4	11	6	0	6 (29)
Thrombocytopenia	8	2	5	0	5 (24)
Non-hematological toxicity					
Bilirubin	3	1	3	1	4 (19)
AST	7	8	3	1	4 (19)
ALT	5	6	3	2	5 (24)
Creatinine	6	4	0	0	0
Fatigue	11	8	0	0	0
Anorexia	2	12	5	0	5 (24)
Nausea	4	9	7	0	7 (33)
Vomiting	7	10	0	0	0
Diarrhea	2	0	0	0	0
Mucositis	1	0	0	0	0
Alopecia	4	14	—	—	—
Neurological sensory	1	0	0	0	0
Febrile neutropenia	—	—	8	0	8 (38)

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

DISCUSSION

In 1991, Moertel et al. (4) reported an objective response rate of 67% to combined chemotherapy with cisplatin and etoposide in 18 patients with anaplastic neuroendocrine tumors, which are analogous to the currently described extrapulmonary PD-NECs, with a median survival of 19 months. Mitry et al. (5) reported a response rate of 42% and median survival of 15 months in 41 patients with extrapulmonary PD-NECs treated with the same combination regimen. In these reports, not only tumors arising from the hepatobiliary and pancreatic regions, but also from the gastrointestinal, head and neck, and tracheal regions were included as extrapulmonary tumors. To the best of our knowledge, this is the first study of the efficacy of cisplatin plus etoposide focusing solely on tumors arising from the hepatobiliary and pancreatic regions.

In the current study, focusing on primary neuroendocrine tumors arising from the hepatobiliary and pancreatic regions, a response rate of 14% and median survival of 5.8 months were obtained in response to combined cisplatin plus etoposide therapy. Although the response rate and prognosis were extremely poor when compared with those reported by previous studies using the same combination of agents for extrapulmonary PD-NECs, when considering the finding that 75% of the patients showed a $>50\%$ decrease in the serum NSE levels, combined cisplatin plus etoposide may be considered to exert some degree of activity. However, whether this result may be comparable to that obtained with other treatment regimen for hepatobiliary and pancreatic PD-NECs is not yet clear, because few studies until date have reported on the efficacy of other regimens for this disease.

Malignant tumors arising from the hepatobiliary and pancreatic regions metastasize easily to the liver, becoming a typical cause of fatal visceral crisis; this anatomic nature may be one of the reasons for the relatively poor prognosis of these tumors. In fact, liver metastasis is a well-documented poor prognostic factor in patients with neuroendocrine tumors (10–14). The incidence of liver metastasis was 81% in the current study. Moreover, 52% had ascites as evidence of peritoneal dissemination, which is also generally recognized as a poor prognostic factor.

In the studies conducted to date, chemotherapeutic regimens for extrapulmonary PD-NECs have been patterned after those used for SCLC. However, these two entities, SCLC and extrapulmonary PD-NECs, may exhibit some differences at the molecular level. For example, Bcl-2 overexpression is observed at a high rate (75–95%) in SCLC

specimens, whereas only 33% of gastroenteropancreatic PD-NECs show this finding (15,16). Unlike SCLC, extrapulmonary PD-NECs show retention of both the short arms of chromosome 3, as revealed by restriction-fragment-length polymorphism studies and cytogenetic analyses (17). Since such cytogenetic differences between these tumors do exist, their clinical features and outcomes with the same treatment may also eventually diverge.

Neuroendocrine tumors also have other histological components in some cases (15,18–23). Such patients with PD-NECs arising from the gastric, colorectal and pancreatic regions generally have an adenocarcinoma component, whereas esophageal PD-NECs show a squamous cell carcinoma component. Thus, the nature of the non-neuroendocrine components in the PD-NECs also seems to depend on the primary site of the tumors. Two potential cells of origin of PD-NECs have been reported: pre-existing neuroectodermal cells and pluripotent epithelial stem cells, the latter appearing to be the more convincing at present (24–26). This cell of origin of the PD-NECs may explain the intermixing of adenocarcinoma or squamous cell carcinoma components in these tumors. It is well known that adenocarcinomas arising from the hepatobiliary tract and pancreas are less sensitive to chemotherapy and have a poor prognosis compared with adenocarcinomas arising from other organs. Likewise, the theory that PD-NECs arise from pluripotent epithelial stem cells may explain why hepatobiliary and pancreatic PD-NECs are less sensitive to chemotherapy and have a poor prognosis when compared with previous reports for miscellaneous extrapulmonary PD-NECs. In fact, it is interesting that elevated serum CEA and CA19-9 levels were confirmed in 38% of the patients in the current study, as both are widely used tumor markers of adenocarcinoma. In addition, one of these patients showed a partial response to gemcitabine monotherapy started after the detection of progressive disease in response to combined therapy with cisplatin and etoposide. Hence, there is a possibility that the tumor in this case showed a mixed histology consisting of neuroendocrine carcinoma and adenocarcinoma components, and that the adenocarcinoma component was refractory to the combination of cisplatin and etoposide and responsive to gemcitabine monotherapy. This may warrant the use of cytotoxic agents that are effective against both the PD-NEC component and the non-neuroendocrine carcinoma components, depending on the primary sites of the tumors.

In conclusion, the current study showed that the combination of cisplatin and etoposide exerted only marginal antitumor activity and relatively severe toxicity against PD-NECs of the hepatobiliary tract and pancreas, when compared with the treatment outcomes suggested by previous reports for extrapulmonary PD-NECs. The retrospective design of this study poses an inherent limitation. A prospective study is considered to be preferable to confirm the efficacy. Notwithstanding, because PD-NECs have an extremely poor prognosis and unsatisfactory treatment outcomes in response to combined chemotherapy with cisplatin plus etoposide, further development of novel treatment is necessary to improve the prognosis.

Acknowledgement

We thank Keiko Kondo for her invaluable assistance in the preparation of this manuscript.

Conflict of interest statement

None declared.

References

1. Doherty GM. Carcinoid tumors and the carcinoid syndrome. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, editors. *Cancer: Principles and Practice of Oncology.* 8th edn. Philadelphia, PA: Lippincott Williams & Wilkins, Inc. 2008;1721–40.
2. National Comprehensive Cancer Network (NCCN). Neuroendocrine Tumors 2008. http://www.nccn.org.
3. Plockinger U, Rindi G, Arnold R, Eriksson B, Krenning EP, de Herder WW, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology* 2004;80:394–424.
4. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer* 1991;68:227–32.
5. Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufie P, Aparicio T, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer* 1999;81:1351–5.
6. Fjallskog ML, Granberg DP, Welin SL, Eriksson C, Oberg KE, Janson ET, et al. Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. *Cancer* 2001;92:1101–7.
7. Solcia E, Capella C, Kloppel G, Heitz PU, Sobin LH, Rosai J. Endocrine tumours of the gastrointestinal tract. In: Solcia E, Kloppel G, Sobin LH, editors. *World Health Organization International Histological Classification of Tumours. Histological Typing of Endocrine Tumours*. 2nd edn. Berlin, Heidelberg, New York: Springer 2000;61–8.
8. DeLellis RA, Lloyd RV, Heitz PU, Eng C. *World Health Organization classification of tumours, pathology and genetics of tumours of endocrine organs.* Lyon, France: IARC Press 2004.
9. Okamoto H, Watanabe K, Kunikane H, Yokoyama A, Kudoh S, Asakawa T, et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. *Br J Cancer* 2007;97:162–9.
10. Janson ET, Holmberg L, Stridsberg M, Eriksson B, Theodorsson E, Wilander E, et al. Carcinoid tumors: analysis of prognostic factors and survival in 301 patients from a referral center. *Ann Oncol* 1997;8:685–90.
11. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol* 2004;22:4762–71.
12. Madeira I, Terris B, Voss M, Denys A, Sauvanet A, Flejou JF, et al. Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. *Gut* 1998;43:422–7.
13. Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer* 2005;12:1083–92.
14. Bettini R, Boninsegna L, Mantovani W, Capelli P, Bassi C, Pederzoli P, et al. Prognostic factors at diagnosis and value of WHO classification in

a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. *Ann Oncol* 2008;19:903–8.
15. Takubo K, Nakamura K, Sawabe M, Arai T, Esaki Y, Miyashita M, et al. Primary undifferentiated small cell carcinoma of the esophagus. *Hum Pathol* 1999;30:216–21.
16. Brenner B, Tang LH, Klimstra DS, Kelsen DP. Small-cell carcinomas of the gastrointestinal tract: a review. *J Clin Oncol* 2004;22: 2730–9.
17. Johnson BE, Whang-Peng J, Naylor SL, Zbar B, Brauch H, Lee E, et al. Retention of chromosome 3 in extrapulmonary small cell cancer shown by molecular and cytogenetic studies. *J Natl Cancer Inst* 1989;81:1223–8.
18. Wick MR, Weatherby R, Weiland LH. Small cell neuroendocrine carcinoma of the colon and rectum: clinical, histologic, and ultrastructural study and immunohistochemical comparison with cloacogenic carcinoma. *Hum Pathol* 1987;18:9–21.
19. Burke AB, Shekitka K, Sobin LH. Small cell carcinomas of the large intestine. *Am J Clin Pathol* 1991;95:315–21.
20. Ho KJ, Herrera GA, Jones JM, Alexander CB. Small cell carcinoma of the esophagus: evidence for a unified histogenesis. *Hum Pathol* 1984;15:460–8.
21. Maitra A, Tascilar M, Hruban RH, Offerhaus GJ, Albores-Saavedra J. Small cell carcinoma of the gallbladder: a clinicopathologic, immunohistochemical, and molecular pathology study of 12 cases. *Am J Surg Pathol* 2001;25:595–601.
22. Sarsfield P, Anthony PP. Small cell undifferentiated ('neuroendocrine') carcinoma of the colon. *Histopathology* 1990;16:357–63.
23. Brenner B, Shah MA, Gonen M, Klimstra DS, Shia J, Kelsen DP. Small-cell carcinoma of the gastrointestinal tract: a retrospective study of 64 cases. *Br J Cancer* 2004;90:1720–6.
24. Fellegara G, D'Adda T, Pilato FP, Froio E, Ampollini L, Rusca M, et al. Genetics of a combined lung small cell carcinoma and large cell neuroendocrine carcinoma with adenocarcinoma. *Virchows Arch* 2008;453:107–15.
25. Vortmeyer AO, Lubensky IA, Merino MJ, Wang CY, Pham T, Furth EE, et al. Concordance of genetic alterations in poorly differentiated colorectal neuroendocrine carcinomas and associated adenocarcinomas. *J Natl Cancer Inst* 1997;89:1448–53.
26. Motojima K, Furui J, Terada M, Shiogama T, Kohara N, Tsunoda T, et al. Small cell carcinoma of the pancreas and biliary tract. *J Surg Oncol* 1990;45:164–8.