Cancer Chemother Pharmacol (2007) 59:637–642
DOI 10.1007/s00280-006-0306-6

ORIGINAL ARTICLE

Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours?

Emilio Bajetta · Laura Catena · Giuseppe Procopio · Sara De Dosso · Ettore Bichisao · Leonardo Ferrari · Antonia Martinetti · Marco Platania · Elena Verzoni · Barbara Formisano · Roberto Bajetta

Received: 5 May 2006 / Accepted: 27 July 2006 / Published online: 26 August 2006

Abstract
Purpose The aim of this trial was to evaluate the safety and efficacy of oxaliplatin and capecitabine (XELOX) in neuroendocrine tumours' (NETs) treatment.
Methods Forty patients (pts) with advanced NETs were treated. Of these, 13 had untreated poorly differentiated NETs, 27 had well-differentiated NETs in progression after somatostatin analogues. Patients received oxaliplatin e.v. 130 mg/mq i.v. and capecitabine 2,000 mg/mq/die. The primary sites of the disease were: lung (10 pts), pancreas (15 pts), small bowel (8 pts), unknown (1 pt), others (6 pts).
Results In 13 pts with poorly differentiated NETs objective responses (OR) were: 3 PR (23%), 1 SD (7%), 9 PD (70%). Biochemical responses were 11%. In 27 patients with well-differentiated NETs the OR were: 8 PR (30%), 13 SD (48%) and 6 PD (22%). Biochemical and symptomatic responses were 20 and 50%, respectively.
Conclusions The XELOX regimen is effective and tolerated in well-differentiated NETs after progression following somatostatin analogues.

E. Bajetta (✉) · L. Catena · G. Procopio · S. De Dosso · L. Ferrari · A. Martinetti · M. Platania · E. Verzoni · B. Formisano
S.C. Oncologia Medica 2, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian, 1, Milan 20133, Italy
e-mail: emilio.bajetta@istitutotumori.mi.it

E. Bichisao
I.T.M.O. Group, Milan, Italy

R. Bajetta
Pharmacology Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy

Keywords Capecitabine · Chemotherapy · Neuroendocrine tumours · Oxaliplatin · XELOX

Introduction

The WHO classification issued in 2000 [1] divides neuroendocrine tumours (NETs) into four categories: *well-differentiated endocrine tumours* (characterised by a low grade of malignancy); *well-differentiated endocrine carcinoma* (more aggressive due to the presence of metastases); *poorly differentiated* endocrine carcinomas (with a high grade of malignancy and a poor prognosis); and *mixed exocrine–endocrine* tumours. The classification of lung tumours is still based on the paper by Travis et al. [2] who recognized the following four categories: *typical carcinoid, atypical carcinoid, small cell lung cancer and large cell neuroendocrine carcinoma.* Typical carcinoids are generally less aggressive than atypical carcinoids, which are less aggressive than small cell carcinoma (poorly differentiated NETs). However, it has been recently published that the WHO classification enables identification of low-grade NET patients suitable for hormonal treatment, but fails in some cases, especially in patients with visceral metastases and a short disease-free interval [3, 4].

The treatment of NETs is mainly based on their biological characteristics of aggressiveness and functional features, such as symptoms and endocrine markers.

When feasible, radical surgery remains the sole effective approach, whereas in other cases hormonal treatment is of choice for well-differentiated endocrine tumours, and chemotherapy for progressing disease and poorly differentiated NETs.

Experience in previous trials have demonstrated that some drugs, such as cisplatin, etoposide, 5-fluorouracil, streptozotocine, dacarbazine and doxorubicin, have significant antitumoural activity in terms of tumour growth control, biochemical responses and reduction of symptoms.

The partial response rates range from 40 to 60% with a median duration of 6 months with the combination of cisplatin and etoposide in undifferentiated NETs [5, 6]. Thus chemotherapy with platinum compounds is considered the standard treatment for patients with poorly differentiated NETs.

Conversely streptozotocin and 5-fluorouracil or doxorubicin should be the standard treatment for patients with well-differentiated pancreatic NETs previously untreated or progressing during somatostatin analogue treatments [7–11]. The use of interferon alone or in combination with somatostatin analogues is still debated; up to now this drug has shown a partial activity in controlling carcinoid syndrome, but there is no evidence of control on cancer growth [12].

In this trial the combination of capecitabine and oxaliplatin has been used on the basis of scientific research data concerning the use of this combination for the treatment of gastrointestinal cancers and also due to the good safety profile of oxaliplatin in comparison with other platinum derivatives. A noteworthy example is the case report published by Tetzlaff and Ajani [13] of a patient suffering from a metastatic carcinoid tumour who responded to an oxaliplatin-based regimen.

The primary focus of the trial was the response rates including biochemical and symptomatic responses, with a secondary objective to evaluate the time to progression (TTP) and safety.

Methods

Patients

From July 2000 to April 2005, a total of 40 consecutive patients (31 males and 9 females, 38/40 with a PS ≤ 1), 13 with high-grade malignancy NETs, who had not been previously treated, and 27 with low-grade malignancy NETs in progression after first-line therapy with somatostatin analogues, were enrolled in this phase II study. Out of 40 patients, 32 (80%) had metastatic disease and 8 patients had locally advanced disease (20%).

Out of 40 patients, 11 had received therapeutic surgery with a median disease-free interval of 10 months (range 3–58 months). Somatostatin analogues had already been given to 27/40 patients (67.5%).

We have included poorly differentiated neuroendocrine carcinoma, Merkel cell carcinoma and large cell neuroendocrine carcinoma of the lung in the population of high grade of malignancy; in fact, all these tumour histotypes are characterised by particularly aggressive clinical behaviour and poor prognosis.

On the other hand, the population of low-grade malignancy NETs has included well-differentiated neuroendocrine carcinoma and typical and atypical carcinoid of lung, for their relatively indolent course.

The histological diagnosis of well-differentiated or poorly differentiated NETs is based on the WHO criteria.

The sites of the primary tumour were bowel (8 pts), lung (10 pts), pancreas (15 pts), unknown (1 pt) and other sites (6 pts).

Table 1 shows patient characteristics according to histological tumour type. The trial was a multicentre I.T.M.O. (Italian Trial in Medical Oncology) group study and involved three centres, co-ordinated by the Unit of Medical Oncology 2, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

The study was carried out in accordance with the guidelines set out in the Declaration of Helsinki. All

Table 1 Patient characteristics related to histological type

Histological type	Nbr. pts (%)	
	High grade	Low grade
Total patients	13	27
Median age (range; years)	59 (46–70)	61 (28–84)
Gender		
Male	11	20
Female	2	7
Performance status (ECOG)		
0/1	8/3	20/7
2	2	–
Site of primary tumour		
Small bowel	1 (8)	7 (26)
Lung	5 (38)	5 (18)
Pancreas	4 (31)	11 (41)
Stomach	–	1 (4)
Other	3 (23)	2 (7)
Unknown	–	1 (4)
Site of metastases		
<2 sites	3 (23)	11 (41)
≥2 sites	10 (77)	16 (59)
Pathological levels of marker		
Chromogranine A	7 (54)	20 (74)
Carcinoid syndrome		
Absent	12	18
Present	1	9
Diarrhoea	–	5
Flushing	–	6
Others	1	2

patients gave their informed consent and the study was approved by the local bioethics committee.

Treatment plan

The XELOX regimen consisted of the intravenous administration of oxaliplatin 130 mg/mq on day 1 and the oral intake of capecitabine 2,000 mg/mq/die from day 2 to day 15, every 3 weeks. The envisaged treatment plan was up to 6 cycles maximum, if feasible.

A total of 72 cycles were performed (range 1–6 cycles). Twenty patients (52.0%) completed the treatment as scheduled; seven patients (17.5%) withdrew from treatment before the planned tumour assessment.

Evaluation of response

The responses were evaluated according to the I.T.M.O. criteria [12], which consider the tumour growth, the presence/severity of symptoms and the behaviour of specific markers separately.

The first evaluation of response was performed after the first 3 cycles of treatment by evaluating the changes in tumour size (objective response), calculated according to the WHO criteria [14], symptom relief or worsening (symptomatic response) and the changes of tumour marker values (biochemical response). At the end of the treatment program the responses were evaluated following the previously described criteria.

The duration of response was calculated from the first documented complete response (CR), partial response (PR) or stable disease (SD), while TTP and overall survival (OS) were calculated from the starting date of treatment.

Drug safety

Drug safety was analysed by assessing the drug toxicity according to the National Cancer Institute Common Toxicity Criteria (NCI CTC Vers. 2) in all patients treated with at least 1 cycle.

Statistical analysis

This is an open, non-comparative clinical study in which no null hypothesis is being tested. The ultimate aim is to evaluate the efficacy and feasibility of a polychemotherapy regimen in two populations of patients: those affected by metastatic or locally advanced high-grade malignancy NETs, who had not been previously treated, and those affected by low-grade malignancy NETs in progression to first-line treatment with somatostatin analogues.

Secondly, the TTP, the duration of response (DR) and the OS were analysed.

No formal statistical analysis was planned. Clinical, laboratory and subjective data are reported as mean (± standard deviation), median, range and percentage where appropriate. Confidence intervals (95%) were calculated.

Survival and TTP curves were calculated according to the Kaplan–Meier method.

Results

All the 40 patients were evaluated for response and toxicity.

Tumour response

No complete responses occurred; 11 (27.5%) partial responses and 14 (35%) disease stabilization were observed; 15 (37.5%) patients showed disease progression.

The responses for high-grade and low-grade malignancy populations were separately analysed.

In 13 patients with diagnosis of high-grade malignancy no complete responses, 3 (23%) partial responses, 1 stabilization (7%) and 9 (70%) disease progression were reported. All these progressions occurred within the treatment period which lasted up to 6 months.

In the low-grade population (27 patients), 8 (30%) partial responses, 13 (48%) disease stabilization and 6 (22%) disease progression were observed.

In this population disease stabilization lasted 17 months (range 3–39) and partial responses 12 months (range 3–38).

Responses in the low-grade population were also analysed for site of primary tumour: for five lung NETs (typical and atypical carcinoids) there were three (60%) partial responses and one (20%) disease stabilization.

In 11 pancreas NETs 3 (27%) partial responses and 5 (45%) stabilizations occurred and in bowel disease (7 patients), only stable disease was observed (7/7).

Biochemical response

Serum Chromogranine A levels were evaluated in 31 patients with an upper normal limit ≤ 34 U/l. Nine patients did not have CgA evaluation at baseline. Increased serum CgA levels were observed in 27 patients (87%) before treatment and after six chemotherapy cycles there was a normalization of levels in 1 patient, a decrease in 4 (14%) patients and stabilization in 2 (7%) cases.

Patients with biochemical responses showed concordant tumour response.

Subjective response

The effects of XELOX were evaluated in 10 patients with carcinoid syndrome. These patients continued somatostatin analogues during chemotherapy. There was a complete disappearance of the syndrome, with a concomitant tumour response, in five patients (50%), two patients with lung NET and three patients with pancreatic NET, while a reduction of intensity or frequency of episodes occurred in one patient. In four patients (40%) the symptoms did not change. No patient experienced symptom progression during treatment.

Overall survival and time to progression

The median overall survival was 32 months (range 1–44+ months) and the median time to progression was 18 months (range 1–43). The curves of OS and TTP are, respectively, shown in Figs. 1 and 2.

Separate data analysis of low and high-grade malignancy shows (Figs. 3, 4): for the first group of patients a median overall survival of 40 months (range 3–40+) and a TTP of 20 months (range 3–40). In the second group the median overall survival was 5 months (range 1–44+) and a TTP of 4 months (range 1–43).

Tolerability

Nausea and vomiting (12.5%), asthenia (12.5%), paresthesias (12.5%), thrombocytopenia (10%), hand–foot syndrome (5%) and mucositis (5%) were the most frequent Grade I–II adverse effects recorded.

Asthenia Grade III in 7.5% of patients and in 1 patient a Grade IV diarrhoea were observed.

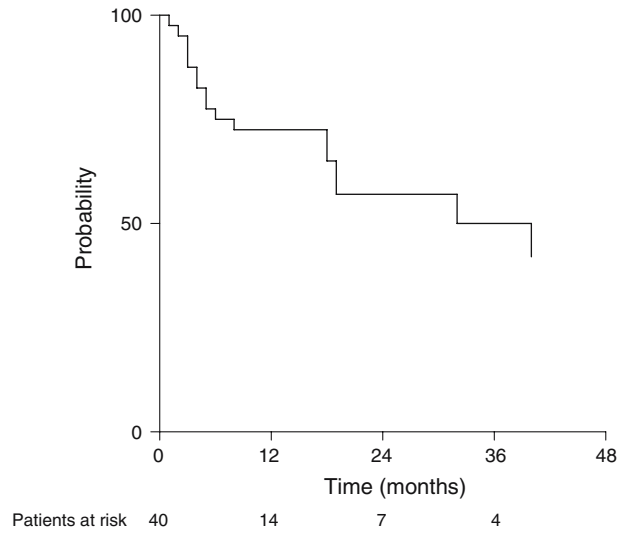

Fig. 1 Overall survival

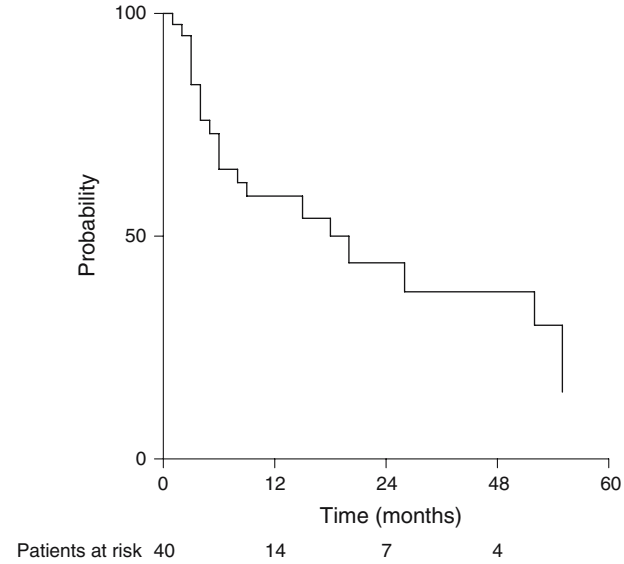

Fig. 2 Time to progression

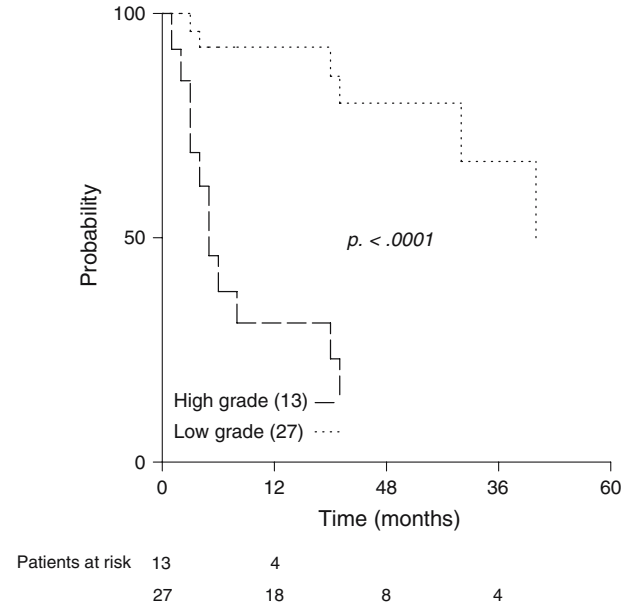

Fig. 3 Overall survival related to histological type

Discussion

Although there is no standard regimen yet for NET treatment, usually poly-chemotherapy with platinum compounds and etoposide is recognised as the gold

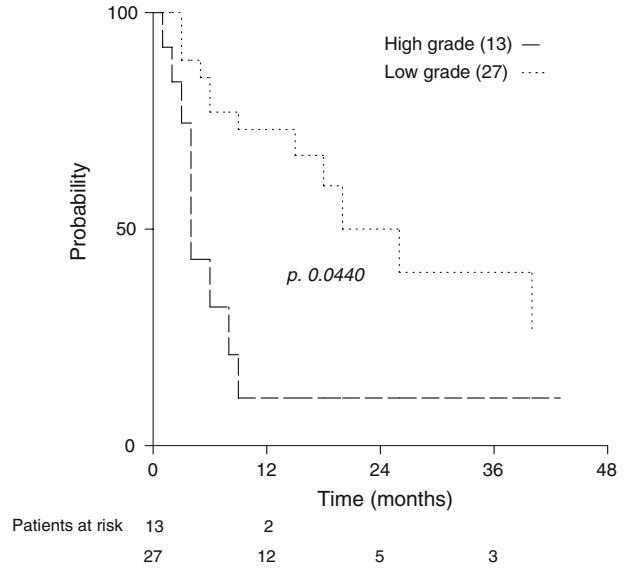

Fig. 4 Time to progression related to histological type

standard for inoperable poorly differentiated NETs with a reported response rate of 60% [6, 15]. In 1991 Moertel et al. [16] suggested the use of this regimen for the treatment of NETs having a high proliferation rate (anaplastic variant). These results were later confirmed; nevertheless in all these studies the authors showed responses only in poorly differentiated disease but not in low-grade malignancies as well as in differentiated carcinoids or islet cell carcinomas (only 7% of tumour response) [6, 17, 18].

So chemotherapy is not considered the first-line treatment for patients with well-differentiated NETs although there are some favourable results using streptozotocine, especially in combination with doxorubicin, in islet cell pancreatic tumours (about 50% of objective responses) [7, 10]. Streptozotocine is not commercially available in Italy and this fact makes its use very difficult.

Other clinical investigations with fluorouracil, dacarbazine and anthracyclines have shown a response rate of <25% in heterogeneous groups of patients (lung and gastro-entero-pancreatic disease and various differentiation grade tumours) [9, 10, 19–22].

The results of these studies show that even though poorly differentiated NETs usually have a good response rate during chemotherapy, they show low sensitivity to the combination of oxaliplatin and capecitabine. These results are in contrast with the data on cisplatin and etoposide, suggesting that not all platinum compounds show similar activity in NETs, and fluorouracil is sometimes ineffective.

On the contrary, patients with low-grade malignancy disease pre-treated with somatostatin analogues and in disease progression can be treated with XELOX regimen and show high response rate. In particular in our series we found satisfactory sensitivity to this regimen in well-differentiated NETs that rapidly progressed to somatostatin analogues (after 3–6 months of treatment), probably due to the different biological profile of these neoplasms compared with well-differentiated and poorly differentiated NETs.

Classification ought to include an intermediate category of NETs (*moderately differentiated NETs*) suggested by the observation that lung and pancreatic tumours show a higher response rate than other sites; in fact in practice, experience shows that these neoplasms are more aggressive than gastro-enteric NETs.

In conclusion XELOX chemotherapy is a good choice of treatment in the case of well-differentiated NETs in the gastro-entero-pancreatic region, not only following somatostatin analogue failure but also in neoadjuvant setting, in order to reduce tumour burden and as pre-surgery protocol (particularly in pancreatic disease). Furthermore, this regimen can be considered for lung NETs (typical and atypical carcinoid) as first-line treatment, considering the high response rate shown, although these data need to be confirmed because of the small number of treated patients with this histological type.

In contrast, these data suggest that the oxaliplatin and capecitabine regimen cannot be considered as a valid alternative to traditional cisplatinum and etoposide treatment for poorly differentiated NETs.

Acknowledgments The authors would like to thank the Italian Trials in Medical Oncology (I.T.M.O.) group for technical assistance, Dr. Stefano Iacobelli (*Università degli Studi "G. D'Annunzio", Chieti, Italy)* and Dr. Alfredo Falcone (*Spedali Riuniti ASL 6, Livorno, Italy*) for cooperation.

References

1. Solcia E, Kloppel G, Sobin LH (2000) Histologic typing of endocrine tumours. WHO international histological classification of tumours. Springer, Berlin Heidelberg New York
2. Travis WD, Brambilla E, Muller-Hermelink HK, Harris SL (2004) Pathology and genetics of tumors of the lung, pleura, thymus and heart. IARC Press, Geneva
3. Bajetta E, Catena L, Procopio G, Bichisao E, Ferrari L, Della Torre S, De Dosso S, Iacobelli S, Buzzoni R, Mariani L, Rosai J (2005) Is the new WHO classification of neuroendocrine tumours useful for selecting an appropriate treatment? Ann Oncol 16:1374–1380
4. Artale S, Giannetta L, Cerea G, Pedrazzoli P, Schiavetto I, Napolitano M, Veronese S, Bramerio E, Gambacorta M, Vanzulli A, Pisconti S, Pugliese R, Siena S (2005) Treatment of metastatic neuroendocrine carcinomas based on WHO classification. Anticancer Res 25:4463–4469
5. Moertel CG, Kvols LK, O'Connell MJ, Rubin J (1991) Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in anaplastic variance of these neoplasm. Cancer 68:227–232

6. Fjallskog ML, Granberg DP, Welin SL, Eriksson C, Oberg KE, Janson ET, Eriksson BK (2001) Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. Cancer 92:1101–1107
7. Rivera E, Ajani JA (1998) Doxorubicin, streptozotocin, and 5-fluorouracil chemotherapy for patients with metastatic islet-cell carcinoma. Am J Clin 21:36–38
8. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D (1992) Streptozocin–doxorubicin, streptozocin–fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 326:519–523
9. Bajetta E, Ferrari L, Procopio G, Catena L, Ferrario E, Martinetti A, Di Bartolomeo M, Buzzoni R, Celio L, Vitali M, Beretta E, Seregni E, Bombardieri E (2002) Efficacy of chemotherapy combinations for the treatment of metastatic neuroendocrine tumours. Ann Oncol 13:614–621
10. Ridolfi R, Amaducci L, Derni S, Fabbri L, Innocenti MP, Vignutelli P (1991) Chemotherapy with 5-fluorouracil and streptozocin in carcinoid tumors of gastrointestinal origin: experiences with 13 patients. J Chemother 3:328–331
11. Gonzalez MA, Biswas S, Clifton L, Corrie PG (2003) Treatment of neuroendocrine tumours with infusional 5-fluorouracil, folinic acid and streptozocin. Br J Cancer 89:455–456
12. Bajetta E, Zilembo N, Di Bartolomeo M, Di Leo A, Pilotti S, Bochicchio AM, Castellani R, Buzzoni R, Celio L, Dogliotti L (1993) Treatment of metastatic carcinoid and other neuroendocrine tumors with recombinant interferon alpha-2. Cancer 72:3099–3105
13. Tetzlaff ED, Ajani JA (2005) Oxaliplatin-based chemotherapy for the treatment of a metastatic carcinoid tumor. Int J Gastrointest Cancer 36:55–58
14. World Health Organization (1979) Handbook for reporting results of cancer treatment. WHO offset publication N. 48, Geneva
15. Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufie P, Aparicio T, Aparicio T, Lasser P, Elias D, Duvillard P, Schlumberger M, Rougier P (1999) Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. Br J Cancer 81:1351–1355
16. Moertel CG, Kvols LK, O'Connell MJ, Rubin J (1991) Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin: evidence of major therapeutic activity in anaplastic variance of these neoplasm. Cancer 68:227–232
17. Oberg K (2001) Chemotherapy and biotherapy in the treatment of neuroendocrine tumours. Ann Oncol 12(Suppl 2):S111–S114
18. Rougier P, Mitry E (2000) Chemotherapy in the treatment of neuroendocrine malignant tumors. Digestion 62:73–78
19. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG (2005) Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group study E1281. J Clin Oncol 22:4897–4904
20. Di Bartolomeo M, Bajetta E, Bochicchio AM, Carnaghi C, Somma L, Mazzaferro V, Visini M, Gebbia V, Tumolo S, Ballatore P (1995) A phase II trial of dacarbazine, fluorouracil and epirubicin in patients with neuroendocrine tumours. A study by the Italian Trials in Medical Oncology (I.T.M.O.) group. Ann Oncol 6:77–79
21. Kulke MH, Stuart K, Enzinger PC, Ryan DP, Clark JW, Muzikansky A, Vincitore M, Michelini A, Fuchs CS (2006) Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol 24:401–406
22. Pavel ME, Baum U, Hahn EG, Hensen J (2005) Doxorubicin and streptozotocin after failed biotherapy of neuroendocrine tumors. Int J Gastrointest Cancer 35:179–185