FOLFIRI regimen: an effective second-line chemotherapy after failure of etoposide–platinum combination in patients with neuroendocrine carcinomas grade 3

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Abstract

Patients with neuroendocrine carcinomas (NECs) grade 3 have a poor prognosis. Etoposide–platinum combination is the standard chemotherapy but the role of a second-line therapy remains unknown. Irinotecan alone or in combination has shown some efficacy in patients treated for small cell lung cancer which had pathological similarities with neuroendocrine tumors. The aim of this study is to determine safety and efficacy of the FOLFIRI regimen in patients with NECs grade 3 after failure of etoposide–platinum combination. This study was retrospective, including patients with NECs grade 3 and treated with the FOLFIRI regimen after progression or toxicity of etoposide–platinum combination in first-line. Patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥ 3 and/or serum alkaline phosphatase $\geq 5 \times$ upper limit of normal value (ULN) and/or bilirubin $\geq 1.5 \times$ ULN were excluded. Among 39 patients who failed etoposide–platinum combination, 19 (49%; 12 women, median age 53 (29–78) years) received the FOLFIRI regimen with a median number of 6 (1–16) courses. Six patients (31%) had at least one episode of grades 3–4 toxicity (neutropenia, $n=3$; diarrhea, $n=3$) without toxic death. Six patients (31%) had objective response, 6 (31%) stable disease, and 7 (38%) tumor progression. Median progression-free survival under FOLFIRI was 4 months. Overall survival was 18 vs 6.8 months in noneligible patients. FOLFIRI regimen is a safe and potentially efficient chemotherapy given as second-line in patients with NECs grade 3 who remain in good condition and with correct liver tests after failure of etoposide–platinum combination. These results should be confirmed in a future prospective study.

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Introduction

Malignant digestive neuroendocrine tumors (NETs) are rare with heterogeneous natural history (Yao *et al.* 2008). Major prognostic factors are tumor differentiation, Ki-67 index, and presence of liver metastases (Madeira *et al.* 1998, Panzuto *et al.* 2005, Hentic *et al.* 2011). Most digestive NETs are well differentiated; and even when the disease is metastatic, prognosis remains good with a 5-year overall survival of 60–90% (Madeira *et al.* 1998, Panzuto *et al.* 2005, Hentic *et al.* 2011). Several treatment modalities are available, than

can be adapted to the type of primary, functional status, tumor evolutivity, and tumor spread. Whenever possible, surgery has to be considered first and when it is not feasible, chemotherapy is proposed to patients with progressive disease or with large liver burden ($\geq 50\%$; Steinmuller *et al.* 2008). In case of malignant well-differentiated NETs, tumor growth is slow and tumor response rate with chemotherapy is usually low. Poorly differentiated endocrine carcinomas (PDECs) are very rare as they represent only 5–10% of digestive NETs (Nilsson *et al.* 2006, Ahlman *et al.*

2008, Bettini *et al.* 2008). At the time of diagnosis, patients are generally in poor condition due to aggressive and diffuse disease. These tumors are characterized by aggressive histological features (high Ki-67 index, extensive necrosis, and nuclear atypia) and are classified as neuroendocrine carcinomas (NECs) grade 3 according to the new World Health Organization (WHO) 2010 classification (Rindi *et al.* 2010). Etoposide–platinum combination is the gold standard for NECs grade 3, with a major antitumoral activity and high tumor response rates (41–67%) reported in the main series published in the 1990s (Moertel *et al.* 1991, Mitry *et al.* 1999, Fjallskog *et al.* 2001). However, prognosis is poor with median progression-free survival of 9 months and median overall survival of 15–19 months. In this rare type of tumor, the potential role of second-line chemotherapy is unknown (Moertel *et al.* 1991, Mitry *et al.* 1999, Fjallskog *et al.* 2001). Combination of 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI) appeared to be of limited efficacy in malignant well-differentiated pancreatic NETs (Ducreux *et al.* 2006, Brixi-Benmansour *et al.* 2011) but irinotecan-based regimens have demonstrated promising antitumoral activity in small cell lung cancer, which share similar pathological features (Langer 2001b, Noda *et al.* 2002). The aim of our retrospective study was to assess the feasibility, tolerance, and efficacy of FOLFIRI regimen as second-line treatment after failure of etoposide–platinum combination in a large monocentric series of patients with NECs grade 3.

Patients and methods

Selection of patients

All consecutive patients with NECs grade 3 were included in this retrospective study in the Pancreatology and Gastroenterology Department of Beaujon University Hospital between 09/2000 and 10/2010. Median follow-up from the diagnosis was 29 (1.6–30.5) months.

The diagnosis of NECs grade 3 was performed by a single pathologist with experience in digestive NET by both histology and immunohistochemistry techniques (neuron-specific enolase, chromogranin A, and Ki-67 expression were at least required for each case) and classified according to the WHO 2010 classification (Rindi *et al.* 2010).

All patients with equivocal pathological diagnosis, that is, mixed tumors (MANEC according to the WHO 2010 classification), histologically well-differentiated neoplasms with Ki-67 >20%, or poorly differentiated

nonendocrine carcinomas with no expression of neuroendocrine markers were excluded (Rindi *et al.* 2010).

The primary tumor and distant metastases were localized in all patients using abdominal and thoracic computed tomography (CT) scan and somatostatin receptor scintigraphy (SRS) and/or positron emission tomography with 18 fluorodeoxyglucose. Endoscopic ultrasonography of the duodenopancreatic area, upper and lower gastrointestinal endoscopy examinations were performed when necessary.

Treatment was decided during a weekly multidisciplinary board dedicated to NETs. In patients with unresectable NEC grade 3, a first-line chemotherapy consisted of a combination of etoposide–platinum salt (etoposide 100 mg/m² on days 1, 2, and 3 plus cisplatin 45 mg/m² on days 2 and 3 every 28 days or carboplatin area under curve (AUC) 5 on day 1 every 21 days). After progression or toxicity (mainly neurotoxicity > grade 2) requiring treatment discontinuation, FOLFIRI regimen was proposed as second-line therapy as a systematic policy apart from 09/2000.

Criteria for treatment initiation are as follows: ECOG performance status 0–2, alkaline phosphatase <5× the upper limit of normal value (ULN), bilirubin <1.5×ULN, creatinin clearance >60 ml/min, neutrophil count >1500/ml, platelet count >100 000/ml, and albumin >28 g/l. When one of these criteria was not fulfilled, best supportive care (BSC) was decided.

Treatment

FOLFIRI combination consisted of irinotecan 180 mg/m² on day 1, followed by 400 mg/m² folinic acid in a 2-h infusion, a 10-min bolus of 400 mg/m² 5-FU, and 1200 mg/m² 5-FU in a 44-h infusion (days 1 and 2) every 14 days. Antiemetic prophylaxis using metoclopramide, ondansetron, and methylprednisolone was systematically proposed and was reinforced when necessary.

Patients who received at least one cycle of FOLFIRI were considered eligible for the study. Chemotherapy was stopped in case of unacceptable/life-threatening adverse event, performance status deterioration (i.e. ECOG ≥3), hepatic laboratory tests worsening, and/or tumor progression on imaging.

Safety and efficacy

Baseline assessment included medical history, physical examination with evaluation of ECOG performance status, and biological tests (blood cell count, serum creatinin and creatinin clearance according to Cockcroft-Gault formula, bilirubin, alkaline phosphatase). During the treatment period, blood tests, evaluation of toxicity,

and physical examination were performed before each cycle.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2. Chemotherapy was delayed in case of $\geq$ grade 2 toxicity; doses of irinotecan and 5-FU (short and long infusion) were reduced by 20% in case of $\geq$ grade 3 diarrhea or $\geq$ grade 3 neutropenia/thrombopenia.

Tumor response rate was assessed by CT scan at 3-month intervals according to Response Evaluation in Solid Tumors (RECIST) criteria (Therasse *et al.* 2000). The best response was considered among all response assessments. Evaluation procedures were performed ahead of schedule if patient's general condition deteriorated or severe toxicity occurred.

Overall survival was calculated from the day of diagnosis of NEC grade 3 to the day of death. For patients receiving FOLFIRI regimen, progression-free survival was calculated from the day 1 of first chemotherapy cycle until clinical and/or morphological progression. This study was approved by the Institutional Review Board of Beaujon Hospital.

Statistical analysis

Quantitative data were expressed as medians (range). Survival rates were calculated according to the Kaplan–Meier method.

Results

General patient characteristics

After a median number of six courses (1–16), etoposide–platinum combination was discontinued in 39 patients due to tumor progression ($n=34$) or severe neurotoxicity ($n=5$). Among them, 19 (49%) were eligible for FOLFIRI regimen; in 14 patients, this switch was decided due to a progressive disease and in the remaining five patients, due to a toxicity of the platinum regimen. Fifteen patients were not eligible due to their poor general condition (ECOG ≥ 3) and five patients, due to severe cholestasis. There were 12 women and seven men with a median age of 53 (29–78) years and with a performance status of 0–1 ($n=14$) or 2 ($n=5$). The site of primary tumor was pancreas ($n=10$), liver ($n=6$), anorectal ($n=2$), or pelvic ($n=1$). All patients had metastatic disease except one who had a locally advanced pancreatic carcinoma. The median Ki-67 index was 50% (21–100%). Median number of FOLFIRI courses was 6 (1–16). Treatment was started with reduced dose (-20% irinotecan) in 5 (26%) patients due to abnormal liver tests ($n=3$) or poor general condition ($n=2$). FOLFIRI was stopped in 16 patients (84%) due to clinical or radiological progression and in one due to grades 3–4 hematological toxicity. Treatment was still going on in two patients at the time of analysis (Table 1).

Table 1 Clinicopathological and somatostatin receptor scintigraphy features in the 19 patients with neuroendocrine carcinoma grade 3 treated with FOLFIRI regimen

Patients	Age	Sex	ECOG performance status	Primary site	Ki-67 (%)	Type of cells	CgA stain positivity	Somatostatin receptor status	SRS
1	45	F	0/1	Liver	80	S	0	ND	N
2	50	F	0/1	Anus	100	S	Strong	0	N
3	53	M	2	Pancreas	50	ND	ND	ND	ND
4	58	F	0/1	Liver	40	S	Weak	Weak	ND
5	54	F	0/1	Pancreas	30	S	0	ND	N
6	56	F	0/1	Pelvic	>20	S	0	0	ND
7	48	M	0/1	Pancreas	50	L	Strong	ND	P
8	44	M	0/1	Liver	50	L	Strong	0	N
9	55	F	0/1	Liver	>20	S	Weak	0	ND
10	78	F	2	Anus	>20	S	Strong	0	ND
11	35	M	2	Pancreas	40	ND	ND	ND	N
12	72	F	2	Pancreas	25	L	Strong	0	N
13	57	F	0/1	Liver	90	S	Weak	0	ND
14	68	M	2	Pancreas	80	S	Strong	ND	ND
15	29	M	0/1	Pancreas	>20	L	Strong	ND	ND
16	37	F	0/1	Pancreas	50	L	Strong	ND	P
17	51	F	0/1	Pancreas	50	L	Strong	0	N
18	47	M	0/1	Pancreas	80	S	Strong	ND	ND
19	61	F	0/1	Liver	40	S	Weak	0	N

CgA, chromogranin A; SRS, somatostatin receptor scintigraphy; ND, not done; L, large; S, small; P, positive; N, negative.

Table 2 Safety and efficacy of FOLFIRI regimen in the 19 patients with neuroendocrine carcinoma grade 3

Patients	Prior therapy	Duration of prior therapy (number of cycles)	Reason for FOLFIRI	Delay between diagnosis and FOLFIRI administration (months)		Toxicity of FOLFIRI (grades 3–4)	Tumor response rate	Overall survival (months)	PFS (months)
1	VP16-cisplatin	6	T	7			SD	16	7
2	VP16-carboplatin	9	P	15	Neutropenia		SD	26	7
3	VP16-cisplatin	4	P	7			SD	12	5
4	VP16-cisplatin and VP16-carboplatin	8	P	11			PD	20	3
5	VP16-cisplatin	6	P	8			OR	18	8
6	VP16-cisplatin	4	P	11			PD	15	3
7	VP16-cisplatin	4	P	5			SD	14	5
8	VP16-cisplatin and VP16-carboplatin	12	P	16			PD	22	3
9	VP16-cisplatin	5	T	11		Neutropenia	OR	22	4
10	VP16-carboplatin	11	P	10	Neutropenia		SD	16	2
11	VP16-cisplatin and VP16-carboplatin	15	P	24			PD	25	1
12	VP16-cisplatin	3	P	10	Diarrhea		OR	Alive	On going
13	VP16-cisplatin	6	T	9			PD	19	3
14	VP16-cisplatin	3	P	4			OR	11	6
15	VP16-cisplatin and VP16-carboplatin	12	P	11			OR	18	6
16	VP16-cisplatin and VP16-carboplatin	10	T	12	Diarrhea		OR	Alive	On going
17	VP16-cisplatin	6	T	18			SD	28	7
18	VP16-cisplatin	3	P	4	Diarrhea		PD	12	2
19	VP16-cisplatin and VP16-carboplatin	8	P	18			PD	19	1

SD, stable disease; OR, objective response; PD, progressive disease; P, progression; T, toxicity.

Safety evaluation

Six patients (32%) had a grades 3–4 toxicity requiring dose reductions. Among them, four patients experienced at least one episode of grade 3 toxicity (neutropenia, $n=1$; diarrhea, $n=3$) and two developed grade 4 neutropenia without fever. Chemotherapy was stopped in one of them due to the occurrence of repeated grades 3–4 neutropenia despite the administration of granulocyte colony stimulating factor (G-CSF). No death occurred due to toxicity (Table 2).

Tumor response rate

Among the 19 patients treated with the FOLFIRI regimen, 6 (31%) had objective response (OR), 6 (31%) stable disease (SD), and 7 (38%) disease progression. Disease control (OR+SD) was achieved in eight of the 14 patients (57%) who received FOLFIRI after progression with etoposide–platinum combination (Table 2).

Survival

Median overall survival of the whole population ($n=39$) was 14 months (1.6–30). In patients being not eligible for second-line treatment with FOLFIRI and receiving BSC, median overall survival was 6.8 months (1.6–30). Median overall survival of patients who received the FOLFIRI regimen ($n=19$) was 18 months (10.5–28) with a median progression-free survival of 4 months (0.5–7.5; Fig. 1; Table 2).

Discussion

NECs grade 3 are very rare tumors with an incidence of 2–1 000 000 inhabitants per year (Ahlman *et al.* 2008, Yao *et al.* 2008). They represent only 5–10% of neuroendocrine neoplasms (Nilsson *et al.* 2006, Bettini *et al.* 2008). This series is the first one that suggests a potential efficacy of FOLFIRI regimen as second-line chemotherapy in patients with digestive NECs grade 3. In this monocentric retrospective study, an OR rate was

Figure 1 Progression-free survival in patients with neuroendocrine carcinoma grade 3 treated with FOLFIRI regimen.

obtained in 31% of patients, and the rate of disease control was 62%. The median progression-free survival and the overall survival were 4 and 18 months respectively. A relatively high proportion of patients (32%, $n=6$) were considered to have a liver primary as previously described by Hainsworth *et al.* (2006). This may be due to the necessity to begin chemotherapy promptly without an exhaustive search of the primary tumor.

First-line chemotherapy with etoposide–cisplatin is the standard regimen for NECs grade 3, however, data about potentially efficient second-line treatments are lacking (Nilsson *et al.* 2006, Ahlman *et al.* 2008, Strosberg *et al.* 2010). Efficacy of irinotecan was demonstrated in colorectal cancer with two dose-limiting toxicities, late diarrhea and febrile neutropenia (Cunningham *et al.* 1998, Rougier *et al.* 1998). This drug has two main metabolic pathways that predominantly take place in the liver; administration to patients with liver dysfunction remains a problem and total bilirubin level has been shown to predict the probability of severe neutropenia (Mathijssen *et al.* 2001, Raymond *et al.* 2002). Conversely, irinotecan- or topotecan-based regimens have demonstrated efficacy in lung cancer, especially in small cell lung cancer which share some similarities with PEDCs. Noticeably in a large randomized trial in 154 patients with extensive small cell lung cancer, irinotecan and cisplatin provided higher overall survival rate compared with etoposide and cisplatin (Langer 2001a, Noda *et al.* 2002). Moreover, intravenous topotecan is currently the second-line agent of choice in patients with small cell lung cancer (O'Brien *et al.* 2007). In a French series of 20 patients with malignant pancreatic well-differentiated NETs treated in first-line, FOLFIRI regimen did not show major antitumoral activity as first-line therapy with a tumor control rate of 75% at 6 months and only one OR (Brix-Benmansour *et al.* 2011). In our study, 20 of the 39 patients were not eligible for FOLFIRI regimen as second-line therapy due to poor general condition or severe cholestasis due to major liver involvement. These two contraindications are not rare in patients with digestive NECs grade 3 due to the aggressiveness of the disease. Likewise, this accounts for the necessity of dose reduction at first irinotecan infusion in five of the 19 patients.

Median overall survival of our whole population (14 months) is in accordance with previous reports about efficacy of etoposide–platinum combination (Moertel *et al.* 1991, Mitry *et al.* 1999). In our series, overall survival in non eligible patients for FOLFIRI was short (6.8 months) due to the disease severity that precluded administration of a second-line therapy.

In contrast, the overall survival of patients treated with FOLFIRI was definitely encouraging (18 months). However, a discrepancy between this result and the short progression-free survival (4 months) could appear somewhat surprising. One hypothesis is that after FOLFIRI withdrawal in case of progression, many patients remain in acceptable condition and can benefit from a subsequent antitumoral treatment. Otherwise, these patients likely have a favorable natural history and a slow tumor growth.

Six of the 19 patients who were able to receive the FOLFIRI regimen experienced OR (rate: 31%) and six had SD (rate: 31%). The disease control rate (62%) appeared to be promising knowing that patients with this tumor type usually experience prompt general status deterioration after failure of first-line chemotherapy. In addition, seven patients achieved an OR or SD (disease control rate of 57%) while they had tumor progression under etoposide–platinum combination.

Recently, promising results using temozolomide-based chemotherapy (alone or in combination with capecitabine ± bevacizumab) as second-line in 25 patients with NECs grade 3 were reported (Welin et al. 2011). The response rate was quite similar to that of observed in our study with one complete response and seven partial responses (overall response rate of 33%) and a median progression-free survival of 6 months. Median survival from initial diagnosis was 22 months (22–42). It is possible that this better result was due to a selection of patients in good condition. Furthermore, 14 of these 25 patients had positive SRS and 12 had an NEC grade 3 with a Ki-67 index between 21 and 30%. These two features are usually associated with a better prognosis (Welin et al. 2011). In our series, among the 19 patients treated in second-line therapy, 13 patients had a Ki-67 index > 30% (68%), five (26%) had an ECOG performance status of 2, and only two SRS were positive among the 10 performed.

Main side effects were neutropenia and diarrhea (grades 3–4, 32%) similar to the patients with colorectal cancer receiving FOLFIRI (Cunningham et al. 1998, Rougier et al. 1998). Though there was no toxic death in our series, a careful management of these toxicities is required with dose adaptation and/or easy use of G-CSF. Only one patient discontinued this regimen due to recurrent grades 3–4 neutropenia.

Our study is the first report on the antitumoral activity and the feasibility of the FOLFIRI regimen administration as second-line chemotherapy in patients with NECs grade 3 and acceptable general condition without severe cholestasis. Since the presentation of these results, the French guidelines have integrated this regimen as being an option after etoposide–platinum

combination failure (<http://www.snfge.asso.fr>). The FOLFIRI regimen should be now tested in a prospective multicenter trial.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- Ahlman H, Nilsson O, McNicol AM, Ruzsniwski P, Niederle B, Ricke J, Jensen R, Kos-Kudla B, Oberg K, O'Connor JM et al. 2008 Poorly-differentiated endocrine carcinomas of midgut and hindgut origin. *Neuroendocrinology* **87** 40–46. (doi:10.1159/000109976)
- Bettini R, Boninsegna L, Mantovani W, Capelli P, Bassi C, Pederzoli P, Delle Fave GF, Panzuto F, Scarpa A & Falconi M 2008 Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. *Annals of Oncology* **19** 903–908. (doi:10.1093/annonc/mdm552)
- Brixi-Benmansour H, Jouve JL, Mitry E, Bonnetain F, Landi B, Hentic O, Bedenne L & Cadiot G 2011 Phase II study of first-line FOLFIRI for progressive metastatic well-differentiated pancreatic endocrine carcinoma. *Digestive and Liver Disease* **43** 912–916. (doi:10.1016/j.dld.2011.07.001)
- Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L et al. 1998 Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* **352** 1413–1418. (doi:10.1016/S0140-6736(98)02309-5)
- Ducreux MP, Boige V, Lebouilleux S, Malka D, Kergoat P, Dromain C, Elias D, de Baere T, Sabourin JC, Duvillard P et al. 2006 A phase II study of irinotecan with 5-fluorouracil and leucovorin in patients with pretreated gastroenteropancreatic well-differentiated endocrine carcinomas. *Oncology* **70** 134–140. (doi:10.1159/000093004)
- 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. (doi:10.1002/1097-0142(20010901)92:5<1101::AID-CNCR1426>3.0.CO;2-V)
- Hainsworth JD, Spigel DR, Litchy S & Greco FA 2006 Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine

- carcinoma: a Minnie Pearl Cancer Research Network Study. *Journal of Clinical Oncology* **24** 3548–3554. (doi:10.1200/JCO.2005.05.0575)
- Hentic O, Couvelard A, Rebours V, Zappa M, Dokmak S, Hammel P, Maire F, O'Toole D, Levy P, Sauvanet A *et al.* 2011 Ki-67 index, tumor differentiation, and extent of liver involvement are independent prognostic factors in patients with liver metastases of digestive endocrine carcinomas. *Endocrine-Related Cancer* **18** 51–59. (doi:10.1677/ERC-09-0319)
- Langer CJ 2001a The emerging world role of irinotecan in lung cancer. *Oncology* **15** 15–21.
- Langer CJ 2001b Treatment of non-small-cell lung cancer in North America: the emerging role of irinotecan. *Oncology* **15** 19–24.
- Madeira I, Terris B, Voss M, Denys A, Sauvanet A, Flejou JF, Vilgrain V, Belghiti J, Bernades P & Ruszniewski P 1998 Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. *Gut* **43** 422–427. (doi:10.1136/gut.43.3.422)
- Mathijssen RH, van Alphen RJ, Verweij J, Loos WJ, Nooter K, Stoter G & Sparreboom A 2001 Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). *Clinical Cancer Research* **7** 2182–2194.
- Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufie P, Aparicio T, Aparicio T, Lasser P, Elias D, Duvillard P *et al.* 1999 Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *British Journal of Cancer* **81** 1351–1355. (doi:10.1038/sj.bjc.6690325)
- 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 the anaplastic variants of these neoplasms. *Cancer* **68** 227–232. (doi:10.1002/1097-0142(19910715)68:2<227::AID-CNCR2820680202>3.0.CO;2-I)
- Nilsson O, Van Cutsem E, Delle Fave G, Yao JC, Pavel ME, McNicol AM, Sevilla Garcia MI, Knapp WH, Kelestimur F, Sauvanet A *et al.* 2006 Poorly differentiated carcinomas of the foregut (gastric, duodenal and pancreatic). *Neuroendocrinology* **84** 212–215. (doi:10.1159/000098013)
- Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, Fukuoka M, Mori K, Watanabe K, Tamura T *et al.* 2002 Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *New England Journal of Medicine* **346** 85–91. (doi:10.1056/NEJMoa003034)
- O'Brien M, Eckardt J & Ramlau R 2007 Recent advances with topotecan in the treatment of lung cancer. *Oncologist* **12** 1194–1204. (doi:10.1634/theoncologist.12-10-1194)
- Panzuto F, Nasoni S, Falconi M, Corleto VD, Capurso G, Cassetta S, Di Fonzo M, Tornatore V, Milione M, Angeletti S *et al.* 2005 Prognostic factors and survival in endocrine tumor patients: comparison between gastro-intestinal and pancreatic localization. *Endocrine-Related Cancer* **12** 1083–1092. (doi:10.1677/erc.1.01017)
- Raymond E, Boige V, Faivre S, Sanderink GJ, Rixe O, Vernillet L, Jacques C, Gattineau M, Ducreux M & Armand JP 2002 Dosage adjustment and pharmacokinetic profile of irinotecan in cancer patients with hepatic dysfunction. *Journal of Clinical Oncology* **20** 4303–4312. (doi:10.1200/JCO.2002.03.123)
- Rindi G, Klimstra DS, Arnold R, Klöppel G, Bosman FT & Komminoth P 2010 Nomenclature and classification of neuroendocrine neoplasms of the digestive system WHO classification of tumours of the digestive system. In *WHO Classification of Tumours of the Digestive System*, 4th edn. WHO: Lyon, France.
- Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J *et al.* 1998 Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* **352** 1407–1412. (doi:10.1016/S0140-6736(98)03085-2)
- Steinmuller T, Kianmanesh R, Falconi M, Scarpa A, Taal B, Kwekkeboom DJ, Lopes JM, Perren A, Nikou G, Yao J *et al.* 2008 Consensus guidelines for the management of patients with liver metastases from digestive (neuro)endocrine tumors: foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* **87** 47–62. (doi:10.1159/000111037)
- Strosberg JR, Coppola D, Klimstra DS, Phan AT, Kulke MH, Wiseman GA & Kvols LK 2010 The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. *Pancreas* **39** 799–800. (doi:10.1097/MPA.0b013e3181ebb56f)
- Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC *et al.* 2000 New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of the National Cancer Institute* **92** 205–216. (doi:10.1093/jnci/92.3.205)
- Welin S, Sorbye H, Sebjornsen S, Knappskog S, Busch C & Oberg K 2011 Clinical effect of temozolomide-based chemotherapy in poorly differentiated endocrine carcinoma after progression on first-line chemotherapy. *Cancer* **117** 4617–4622. (doi:10.1002/cncr.26124)
- Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A *et al.* 2008 One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of Clinical Oncology* **26** 3063–3072. (doi:10.1200/JCO.2007.15.4377)

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