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 ≥ 5 × upper limit of normal value (ULN) and/or bilirubin ≥ 1.5 × 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 (≥ 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. 2011).
Patients and methods
Selection of patients

All consecutive patients with NECs grade 3 were included in this retrospective study in the Pancreatolo-
y 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 neuro-
endocrine 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 multi-
disciplinary 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, neut-
rophil 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 folic 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 Cockroft-
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 ≥ grade 2 toxicity; doses of irinotecan and 5-FU (short and long infusion) were reduced by 20% in case of ≥ grade 3 diarrhea or ≥ 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 Clinopathological and somatostatin receptor scintigraphy features in the 19 patients with neuroendocrine carcinoma grade 3 treated with FOLFIRI regimen

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>ECOG performance status</th>
<th>Primary site</th>
<th>Ki-67 (%)</th>
<th>Type of cells</th>
<th>CgA stain positivity</th>
<th>Somatostatin receptor status</th>
<th>SRS</th>
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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

<table>
<thead>
<tr>
<th>Patients</th>
<th>Prior therapy</th>
<th>Duration of prior therapy (number of cycles)</th>
<th>Reason for FOLFIRI</th>
<th>Delay between diagnosis and FOLFIRI administration (months)</th>
<th>Toxicity of FOLFIRI (grades 3–4)</th>
<th>Tumor response rate</th>
<th>Overall survival (months)</th>
<th>PFS (months)</th>
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<td>6</td>
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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 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 (Brixi-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.

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