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

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Running title: FOLFIRI in neuroendocrine carcinomas grade 3

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Abstract

Patients with neuroendocrine carcinomas grade 3 have a poor prognosis. Etoposide-platinum combination is the standard chemotherapy but the role of a second-line 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.

To determine safety and efficacy of the FOLFIRI regimen in patients with neuroendocrine carcinomas grade 3 after failure of etoposide-platinum combination.

Retrospective study of patients with neuroendocrine carcinomas grade 3 and treated with the FOLFIRI regimen after progression or toxicity of etoposide-platinum combination in first-line. Patients with ECOG performance status ≥ 3 and/or serum alkaline phosphatase ≥ 5 x ULN and/or bilirubin ≥ 1.5 x 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 (32 %) had at least one episode of grade 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 months versus 6.8 months in non eligible patients.

FOLFIRI regimen is a safe and potentially efficient chemotherapy given as second-line in patients with neuroendocrine carcinomas 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.
1. 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 (Hentic et al. 2011; Madeira et al. 1998; Panzuto et al. 2005). 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% (Hentic et al. 2011; Madeira et al. 1998; Panzuto et al. 2005). 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 are very rare as they represent only 5-10% of digestive NETs (Ahlman et al. 2008; Bettini et al. 2008; Nilsson et al. 2006). At 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 Organisation (WHO) 2010 classification (Rindi et al. 2010). Etoposide-platinum combination is the gold standard for NECs grade 3, with a major anti-tumoral activity and high tumor response rates (41-67%) reported in the main series published in the 1990’s (Fjallskog et al. 2001; Mitry et al. 1999; Moertel et al. 1991). 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 (Fjallskog et al. 2001; Mitry et al. 1999; Moertel et al. 1991). Combination of 5-FU,
leucovorin and irinotecan (FOLFIRI) appeared to be of limited efficacy in malignant well-differentiated pancreatic NETs (Brixi-Benmansour et al. 2011; Ducreux et al. 2006) but irinotecan-based regimens have demonstrated promising anti tumoral 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.
2. Patients and methods

2.1. 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, i.e. mixed tumors (MANEC according to the WHO 2010 classification), histologically well-differentiated neoplasms with Ki-67 >20% or poorly-differentiated non endocrine carcinomas with no expression of neuroendocrine markers were excluded (Rindi et al. 2010).

Localization of the primary tumor and of distant metastases was performed in all patients using abdominal and thoracic computed tomography (CT) scan and somatostatin receptor scintigraphy (SRS) and/or positron emission tomography with 18 fluoro-deoxy-glucose.

Endoscopic ultrasonography of the duodenopancreatic area, upper and lower gastro-intestinal 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 in combination of etoposide-platinum salt (etoposide 100 mg/m² on day 1,2, and 3 plus cisplatin 45 mg/m² on day 2 and 3 every 28 days or carboplatin 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 required for treatment initiation as follows: ECOG performance status 0-2, alkaline phosphatase < 5 x the upper limit of normal value (ULN), bilirubin < 1.5 x 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.

2.2. Treatment

FOLFIRI combination consisted of irinotecan 180 mg/m² on day 1, followed by 400 mg/m² folinic acid in a 2-hour infusion, a 10-min bolus of 400 mg/m² 5-fluourouracil (5FU) and 1200 mg/m² 5FU in a 44-hour infusion (day 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 as 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.

2.3. 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 Cockroft, 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 three 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 general condition deteriorated or severe toxicity occurred.

Overall survival was calculated from the day to diagnosis of NEC grade 3 to the date 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 Institution Review Board of Beaujon hospital.

2.4. Statistical analysis

Qualitative data were expressed as numbers and percentages. Quantitative data were expressed as medians [range]. Survival rates were calculated according to the Kaplan-Meier method.
3. Results

3.1. General patient characteristics

After a median number of 6 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 5 remaining patients, 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 7 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 of 50% [21%-100%]. Median number of FOLFIRI courses was 6 [1-16]. Treatment was started with reduced dose (~20% of 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 1 due to grade 3-4 hematological toxicity. Treatment was still on going in two patients at time of analysis (table 1).

3.3. Safety evaluation

Six patients (32%) had a grade 3-4 toxicity requiring dose reductions. Among them, 4 patients experienced at least one episode of grade 3 toxicity (neutropenia n=1, diarrhea n=3) and 2 developed grade 4 neutropenia without fever; chemotherapy was stopped in 1 of them due to the occurrence of repeated grade 3-4 neutropenia despite the administration of G-CSF. No toxic death occurred (table 2).
3.4. 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 (DP). Disease control (OR + SD) was achieved in 7 of the 13 patients (54%) who received FOLFIRI after progression with etoposide-platinum combination (table 2).

3.5. 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 regimen and receiving best supportive care, 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] (figure 1) (table 2).
4. Discussion

NECs grade 3 are very rare tumors with an incidence of 2 to 1,000,000 inhabitants/year (Ahlman et al. 2008; Yao et al. 2008). They represent only 5-10% of neuroendocrine neoplasms (Bettini et al. 2008; Nilsson et al. 2006). This series is the first one which suggests a potential efficacy of FOLFIRI regimen as second-line chemotherapy in patients with digestive NECs grade 3. In this monocentric retrospective study, an objective response rate was obtained in 31% of patients, and the rate of disease control was of 62%. The median progression-free survival and the overall survival were of 4 months 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. This may be due to the necessity to begin chemotherapy promptly without an exhaustive search of the primary tumor (Hainsworth et al. 2006).

Whereas first-line chemotherapy with etoposide-cisplatin is the standard regimen for NECs grade 3, data about potentially efficient second-line treatments are lacking (Ahlman et al. 2008; Nilsson et al. 2006; 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 to 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 1 objective response (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 contra-indications 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 5 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 in this indication (Mitry et al. 1999; Moertel et al. 1991). 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 of a subsequent antitumoral treatment. Otherwise, these patients likely have a favourable natural history and a slow tumor growth.

Six of the 19 patients who were able to receive the FOLFIRI regimen experienced objective response (OR rate: 31%) and 6 had stable disease (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, 7 patients achieved an objective response or stable disease (disease control rate of 68%) 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 observed in our study with 1 complete response and 7 partial responses (overall response rate of 33%) and a median progression-free survival of 6 months. Median survival from initial diagnosis was 32 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 a NEC grade 3 with a Ki-67 index between 21-30%, these two features being 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%), 5 (26%) had an ECOG performance status of 2 and only 2 SRS were positive among the 10 performed.

Main side effects were neutropenia and diarrhea (grade 3-4: 32%) similarly to patients with colorectal cancer receiving FOLFIRI (Cunningham et al. 1998; Rougier et al. 1998). Despite 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 grade 3-4 neutropenia.

Our study is the first report of the anti-tumoral 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

Olivia Hentic declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Bibliography


Table 1: Clinico-pathological and somatostatin receptor scintigraphy features in the 19 patients with neuroendocrine carcinoma grade 3 treated with FOLFIRI regimen.

<table>
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<th>Type of cells (i)</th>
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Legend:
(i) large (L) / small (S)
(ii) positive (P) / negative (N)
Chromogranin A (Cg A)
Somatostatin receptor scintigraphy (SRS)
Not done (ND)
Table 2: Safety and efficacy of FOLFIRI regimen in the 19 patients with neuroendocrine carcinoma grade 3.

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Legend:
(i) VP16-cisplatin (1) / VP16-carboplatin (2)
(ii) progression (P) / toxicity (T)
(iii) stable disease (SD) / objective response (OR) / progressive disease (PD)
Figure 1: Progression-free survival in patients with neuroendocrine carcinoma grade 3 treated with FOLFIRI regimen