Original article

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Efficacy of a chemotherapy combination for the treatment of metastatic neuroendocrine tumours

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Objectives: Neuroendocrine tumours (NETs) are heterogeneous neoplasms for which there is no standard treatment. We have previously proposed an effective polychemotherapy (5-fluorouracil, dacarbazine and epirubicin), which only produced objective responses of brief duration. The present study aimed to assess in a multidisciplinary manner the efficacy of the same regimen at intensified doses in patients with advanced NETs.

Patients and methods: Eighty-two consecutive patients entered the study, of whom 21 had inoperable, locally advanced disease and 61 had metastatic disease. Seventy-two patients were evaluated for objective, biochemical and subjective responses. Response rate, time to progression (TTP) and overall survival (OS) were evaluated based on histotype.

Results: An objective response was observed in 20 patients (intention-to-treat and standard analysis 24.4% and 27.8%, respectively). Complete biochemical and subjective responses were obtained in 25.1% and 38.9% of the cases. The median duration of treatment was 4 months and the objective responses had a median duration of 38 months. After a 60-month follow-up the median TTP and OS were 21 and 38 months, respectively.

Conclusions: Our polychemotherapy regimen is effective, with long duration, and is well tolerated both for gastroenteropancreatic and lung NETs, as well as for tumours with a more aggressive clinical behaviour. The new WHO endocrine tumour histotyping, examining also the tumour biology, may give additional information for selecting patients to chemotherapy.

Key words: chemotherapy, chromogranin A, metastatic disease, neuroendocrine tumours

Introduction

Neuroendocrine tumours (NETs) are rare neoplasms originating from cells belonging to either diffuse or confined neuroendocrine systems [1]. These tumours have specific clinical and biological features [2–4]: they generally have a low proliferation rate and the capacity to release biologically active substances responsible for specific syndromes [5, 6]. Moreover, the class of NETs comprises a wide range of neoplasms, each having its own histology and peculiar biological behaviour in terms of both aggressiveness and hormone production. Such heterogeneity makes the medical treatment of NETs difficult and there is no standard therapy, although biotherapy and chemotherapy are considered to be effective in patients with syndromes and advanced disease, respectively.

Radical surgery is the primary curative approach [7, 8], but unfortunately the diagnosis is often delayed due to the slow growth of these tumours and the difficulty in correctly identifying the symptoms related to tumour-released hormones. For this reason, many NET patients do not undergo surgery and need medical treatment for metastatic or inoperable disease.

The role played by somatostatin analogues (octreotide and lanreotide) alone or in combination with interferon-α is well known in functioning tumours [9–11]. Although these molecules seem to be scarcely effective in blocking tumour proliferation, they substantially reduce symptoms related to tumour-induced hormone release. Somatostatin analogues and interferons yield 15% to 20% objective response rates, while the hormone-release suppression rate may be as high as 70% [10].

Systemic chemotherapy is often inadequate for treatment of carcinoid tumours, because these tumours have a well-differentiated histology and low proliferation index. In 1991,

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Moertel et al. [12] suggested the use of chemotherapy for the treatment of NETs having a high proliferation rate (advanced anaplastic neoplasms and pancreatic islet-cell tumours). Streptozotocin and chlorozotocin have been demonstrated to be the most efficacious drugs available for the treatment of NETs, but their nephrotoxicity has reduced their use significantly [13, 14]. 5-Fluorouracil (5-FU) and doxorubicin are less toxic than streptozotocin, but the observed objective response rate is quite low, i.e. ≤25% [15]. Other drugs have been evaluated, either alone or in combination (dacarbazine [15], etoposide and cisplatinum [12, 16]), without satisfactory results being achieved in terms of response duration.

5-FU, dacarbazine and anthracyclines in different combinations have shown the highest response rates and no cross-resistance, because their mechanisms of action do not overlap [17–19]. Our group has conducted clinical trials aimed at evaluating a combination therapy with 5-FU, dacarbazine and epiadriamycin [19, 20]. The use of epiadriamycin rather than doxorubicin was mainly the result of the marketing policies of the pharmaceutical companies producing the two drugs. Doxorubicin and epiadriamycin have an identical spectrum of activity, but in Italy the latter is more readily available than doxorubicin. This polychemotherapy regimen (abbreviated as FDE) produced tumour response rates quite similar to other chemical treatments, and patients displayed good inhibition of the biochemical marker release. The treatment was very well tolerated, but the objective response rate was suboptimal [19].

In order to investigate whether dose intensification could lead to an improvement of the clinical efficacy of the FDE regimen, we decided to test the intensified FDE regimen in patients with progressive, advanced NETs. Overall, objective responses were obtained in 24% of patients and the response rate was higher (30%) in patients with gastroenteropancreatic tumours [20].

This paper describes the evaluation of the efficacy of the intensified FDE regimen in a very large number of patients suffering from NETs. The polychemotherapy activity was assessed in a multidisciplinary manner, because chemotherapy also generally shows very low objective response rates in patients experiencing prolonged survival and a significant reduction in diarrhoea or flushing episodes. In particular, the clinical efficacy of the treatment was assessed by evaluating tumour response, relief of syndromic symptoms and changes in biomarker levels, as well as by calculating time to progression (TTP) and overall survival (OS).

Patients and methods

Patients

Between August 1994 and November 1999, 82 consecutive patients (48 males and 34 females) presented to the Istituto Nazionale per lo Studio e la Cura dei Tumori of Milan for medical treatment of NETs, and were considered eligible for our study.

Uncertain diagnoses were confirmed by our pathologists following review of tumour sections. When the reviewing process was complete, the ultimate histotypes were as follows: 32 foregut tumours, 12 midgut tumours, three hindgut tumours, seven bronchial carcinoids, three Merkel's cell tumours, three medullary thyroid carcinomas (MTCs), two thymus tumours, one paraganglioma and 19 unknown primary site NETs.

Patients with Eastern Cooperative Oncology Group (ECOG) [21, 22] performance status >2, and without adequate bone marrow, renal and hepatic function, were considered ineligible.

The study was carried out according to the Helsinki Declaration. All patients gave their informed consent and the study was approved by the local bioethics committee.

Treatment plan

The FDE regimen (5-FU 500 mg/m^2, dacarbazine 200 mg/m^2, epiadriamycin 30 mg/m^2) was administered intravenously on days 1–3 every 3 weeks for at least three cycles. Treatment was continued until a maximum of nine cycles in those patients who had an objective response after the sixth cycle of polychemotherapy.

Patients with carcinoid syndrome who did not experience any symptom relief after three cycles of chemotherapy were allowed concomitant treatment with somatostatin analogues until the resolution of symptoms.

Intention-to-treat and standard analysis

All of the enrolled patients were considered for intention-to-treat analysis, while patients were excluded from the standard analysis in case of: refusal of therapy, early progression (i.e. before the first clinical assessment), missing follow-up or interruption of therapy immediately after the first administration. The latter applied to patients who spontaneously interrupted treatment after the first cycle even in the absence of progressive disease (PD) or severe adverse effects.

Clinical assessment

The eligible patients were monitored by physical examination and biomarker determination. In addition, ^{111}In-octreotide scintigraphy, ^{m99}Tc-bone scan, ultrasound or computed tomography scan were performed for tumour measurement or assessment. A complete evaluation of the clinical status was carried out at every third cycle of therapy; patients who progressed before the first evaluation were considered not evaluable.

The clinical response [complete response (CR) or partial response (PR)] was assessed considering: (i) changes in tumour size; (ii) changes in biomarker levels; and (iii) symptom relief or worsening. Tumour response was defined according to the criteria of the International Union Against Cancer [23]. The biochemical and symptomatic responses had been characterized previously [24].

Clinical benefit/overall success was defined by an objective tumour response or no change (NC) status lasting for >6 months. All of the patients with NC status lasting <6 months were considered as progressing patients.

In the case of objective response, some patients were proposed for surgical resection. In the case of radical surgery after polychemotherapy, patients were considered to be disease-free when: (i) there was no evidence of metastases or local recurrence, assessed by radiology, ultrasonography or scintigraphy; (ii) the surgical margins were judged tumour-negative by the pathologist.

The duration of response was calculated from the first documented CR or PR, while TTP and OS were calculated from the starting date of therapy.

Drug safety

Drug safety was evaluated by assessing drug toxicity according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) [25] in all patients treated with at least one cycle.

Dose adjustements at the start of a subsequent course of therapy were based on nadir counts or maximal non-haematological toxicity from the preceding course of therapy. Absolute neutrophil counts had to be $>1.5 \times 10^9$/l and platelets $>100 \times 10^9$/l prior to the start of any cycle. After a 1-week delay, patients could be re-treated every 4 weeks without dose reduction. After a 2-week delay, patients could be given FDE with a 50% dose. If neutrophils had not exceeded 1.5×10^9/l or platelets had not exceeded 100×10^9/l after a 2-week delay, the patient was removed from the study and considered to have had unacceptable toxicity. For non-haematological adverse effects of NCI CTC grade ≥1, the drugs have to be withheld until there is a resolution to a grade ≤1 before proceeding. Treatment could restart at a 25% dose reduction if indicated by the treating physician.

Specimen collection and analytical methods

In most patients, plasma chromogranin A (CgA), serum neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), serum calcitonin (Ct) and urine 5-hydroxy-3-indole acetic acid (5-HIAA) were determined at baseline and at each clinical evaluation.

Peripheral blood was collected by venipuncture on the day of therapy prior to drug administration and aliquots of 24 h urine samples were also collected. Patients were instructed not to eat bananas, pineapples or nuts, or drink tea or coffee, and were not to be given drugs containing methyl-dopa or sympathicomimetic amines at least 3 days before the start of urine sampling.

All of the biomarker measurements were carried out by means of immunoenzymatic or immunoradiometric assays as previously described [26]. All assessments were carried out in duplicate and the tested samples were adequately diluted, if necessary.

Biomarker cut-off values

The values corresponding to the 95th percentile of our series of samples from blood donors were taken as CgA and NSE cut-off levels (34 U/l and 12.5 µg/l for CgA and NSE, respectively). The CEA cut-off value was 5 µg/l and was established on the basis of the 95th percentile of a non-smoking population. For 5-HIAA, we assumed a cut-off level of 10 mg/l in 24 h urine samples.

Statistical analysis

Simple descriptive statistics were used to describe the variables. Quantitative data are reported as means ± standard error of the means (SEM). The studied population was also described by median values and the population dispersion by lowest and highest values. When values diverged from a normal distribution, log transformation was carried out.

TTP and OS were computed using the Kaplan–Meier method and comparison of two groups of survival data by means of the log-rank test [27]. When the relationship between discrete values was examined, χ^2 analysis was performed; the association was estimated by computing phi coefficient, coefficient of contingency (C), and Cramér's V. In all statistical tests performed, a 5% level of significance was used [28].

The software SPSS 6.0 for Windows by SPSS Inc. (Chicago, IL, USA) was used for data management and to perform statistics.

Results

Patients characteristics

Of the 82 enrolled patients, 21 subjects had locally advanced disease and 61 had metastatic disease. Of the metastatic lesions, 51 were located in the liver, 28 in the lymph nodes, 13 in bone, nine in the lungs, one in the mediastinum and one on the skin. Twenty-three patients were previously treated with curative surgery and 29 had had palliative surgery; all patients were chemotherapy naive, but 20 had previously been treated with octreotide (11 cases), interferon-α (one case), radio-therapy (eight cases) or combined medical treatment (one

Table 1. Main patient characteristics

	Number of patients or value
Males/females	48/34
Median age, years (range)	55 (74–23)
Performance status (ECOG scale)	
0	60
1	20
2	2
Site of primary tumour	
Foregut	
Stomach	4
Pancreas	28
Midgut	
Bowel	10
Gall bladder	2
Hindgut	
Colon	1
Rectum	2
Lung	7
Medullary thyroid carcinoma	3
Merkel's cell tumour	3
Others	
Thymus	2
Paraganglioma	1
Unknown	19
Median interval from diagnosis, months (range)	17 (1–130)
Abnormal release of	
Chromogranin A	64%
Neurone-specific enolase	33%
Carcinoembryonic antigen	16%
Calcitonin[a]	45%
5-Hydroxyindoleacetic acid[b]	33%

[a]Evaluated only in medullary thyroid carcinomas.
[b]Evaluated only in enterochromaffin-like cell tumours.

Table 2. Tumour-related syndrome according to tumour

Tumour	Syndromic symptoms			
	Diarrhoea	Flushing	Cardiac disease	Abdominal cramps
Gastroenteropancreatic tract tumour (17 patients)	11	13	3	3
Medullary thyroid carcinoma (one patient)	–	1	–	–

Table 3. Response to treatment: intention-to-treat and standard analysis

Response assessment	Objective response to treatment	
	Intention-to-treat analysis (%)	Standard analysis (%)
Number of patients	82	72
CR	4 (4.9)	4 (5.6)
PR	16 (19.5)	16 (22.2)
NC	33 (40.2)	33 (45.8)
PD/treatment failure	29 (35.4)	19 (26.4)
Clinical benefit/overall success	53 (64.6)	53 (73.6)

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

case). Table 1 shows the main clinical characteristics of the patients. Eighteen patients had tumour-related syndromes. Table 2 illustrates the observed symptoms according to the tumour histotypes.

Intention-to-treat and standard analyses

Overall, 82 consecutive patients were assessed on the basis of the intention-to-treat analysis. Four of them experienced a CR, 16 a PR, 33 NC for ≥6 months, 19 PD, and 10 patients were considered to have failed treatment because of inadequate treatment (administration of less than three cycles of therapy). The latter 10 patients were excluded from the standard analysis. No patient was excluded from the response assessment because of the administration of somatostatin analogues for chemotherapy-unresponsive syndromes.

Overall, 72 patients were considered evaluable for objective, biochemical and subjective responses on the basis of the standard analysis. Table 3 summarises the overall response rate to intensified FDE by both intention-to-treat and standard analyses.

Tumour response according to histotype

Four CRs were observed in patients with foregut, lung and unknown NETs and Merkel's cell tumour; 16 PRs were shown by patients with foregut, midgut and unknown NETs and MTC. Disease stabilisation occurred in 33 patients and PD in 19 patients. Table 4 illustrates these data. It is noteworthy that 32 of 44 patients (72.7%) with foregut, midgut, hindgut and bronchial carcinoids had clinical benefit, as well as 17 of 19 patients (89.5%) with unknown primary site NET and three of nine patients (33.3%) with Merkel cell's carcinoma, MTC or paraganglioma.

A single PR was observed in a MTC patient and two PRs were recorded in unknown primary site NETs. No objective response or disease stabilization was observed in the paraganglioma patient or in patients having thymus NETs.

When classifying patients according to clinical status (CR plus PR, NC status or PD) and the biological aggressiveness of the tumour (foregut, midgut, hindgut and other type of NETs), patients were differently distributed across the frequency classes (χ^2 test = 18.68, P = 0.00091).

Biochemical response

Plasma CgA and serum NSE were measured in all enrolled patients, as these biomarkers have been established to be the most accurate in NET management, independent of the site of the tumour or its ability to release biologically active molecules [29]. Serum CEA and Ct were evaluated in MTC patients and urine 5-HIAA in patients having enterochromaffin-cell tumours or carcinoid syndrome.

In patients without any syndrome, inappropriate biomarker release was observed at baseline in 80.6% of the cases, while at the end of FDE chemotherapy this percentage was reduced to 55.5%. The polychemotherapy proved to be particularly efficacious in completely normalising biomarker production (i.e. in obtaining a biochemical CR) in 25.1% of the patients with altered circulating biomarker levels. In patients suffering from syndromes due to carcinoids or MTC, the former figures were similar (83.3% at baseline versus 50% at the end of therapy), while a CR was achieved in a more relevant percentage (30.3% of cases).

Table 4. Response to treatment: objective response according to histotype

	Objective response to treatment			
	CR	PR	NC	PD
Gastroenteropancreatic tract				
Foregut	1	7	8	6
Midgut	–	6	3	3
Hindgut	–	–	1	2
Other sites				
Lung	1	0	5	1
Medullary thyroid carcinoma	–	1	2	–
Merkel's cell carcinoma	1	–	–	2
Thymus	0	0	0	2
Paraganglioma	0	0	0	1
Unknown	1	2	14	2
Total (percentage calculated on the basis of the standard analysis)	4 (5.6)	16 (22.2)	33 (45.8)	19 (26.4)

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

Variations in plasma CgA levels were studied in those patients who had three or more examinations and a clinical follow-up of ≥6 months. Arbitrarily, we considered as variations only those changes that exceeded the former values by 50%. In 43 patients the results of the biochemical follow-up were as follows. Fourteen patients showing a clinical objective response had stable CgA in two cases, diminishing marker levels in 11 cases and increasing levels in only one case. Of the 19 patients whose disease was clinically classified as a NC status five cases had stable CgA, three cases had rising marker levels and 11 cases decreasing levels. Ten patients who did not respond to the administered therapy showed an increase in CgA in all cases. χ^2 analysis verified the significance of the different patient distributions (χ^2 test = 28.57, P = 0.00001; phi coefficent = 0.82; C coefficent = 0.82; Cramér's V = 0.58).

Subjective response

In the 18 patients with syndromes related to the presence of carcinoids or MTC, we also evaluated the effects of FDE therapy on symptoms. None of these patients needed somatostatin analogue treatment during FDE polychemotherapy. Overall, we observed complete disappearance of the syndrome in seven patients (38.9%), while a reduction in the intensity or frequency of episodes was demonstrable in three subjects (16.7%), and in eight cases there was an NC status (44.4%). It is noteworthy that there were complete symptomatic responses in four carcinoids and three other NETs (pancreas islet cell and lung tumours), and there were three partial symptomatic responses in two carcinoids and one pancreas islet-cell tumour.

Response duration, TTP and OS

The median duration of treatment in the 72 evaluable patients was 4 months (range 3–16 months). The 20 objective responses observed in our patient series had a median duration of 38 months (range 12–47 months). The median time of disease stabilisation was 16 months (range 9–50 months) in the 33 patients assessed as having an NC status.

The overall median TTP was 21 months (range 6–54 months). When patients with classical foregut, midgut, hindgut and lung carcinoids and patients with other NETs (Merkel's cell tumours, MTCs and other ones) were considered separately, TTP did not significantly differ in the two groups (log-rank test = 0.59, P = 0.44).

The median OS in the whole population was 38 months (range 23–60 months). When patients were stratified as previously described, statistical analysis did not demonstrate any difference in the OS of the two groups (log-rank test = 2.12, P = 0.15).

Cytoreductive action of the FDE regimen

Eight of the responders with inoperable disease were subjected to surgery after being given FDE polychemotherapy. The main patient characteristics were as follows: five males and three females; median age 54 years (range 45–69 years); six neuroendocrine carcinomas and two carcinoids (primary sites: pancreas, bowel and unknown).

Radical surgery was achieved in two patients and debulking surgery in another four; in only two patients did surgery prove totally ineffective. One of the two radically treated patients had locally advanced disease and lymph node metastases and the other had liver and lymph node involvement. Both these

Table 5. Treatment toxicity: adverse effects in treated patients (%)

Adverse effect	NCI CTC grade			
	1 (%)	2 (%)	3 (%)	4 (%)
Nausea/vomiting	16 (20)	16 (20)	3 (4)	–
Diarrhoea	7 (9)	4 (5)	–	–
Mucositis	15 (18)	12 (15)	2 (2)	–
Alopecia	2 (2)	7 (10)	29 (36)	20 (27)
Astenia	5 (6)	9 (11)	1 (1)	–
Sepsis	3 (4)	5 (6)	–	–
Anaemia	12 (15)	8 (10)	4 (5)	–
Leukopenia	4 (5)	6 (7)	2 (2)	3 (4)
Neutropenia	3 (4)	10 (12)	10 (12)	9 (11)
Trombocytopenia	3 (4)	1 (1)	2 (2)	–

patients were without any evidence of disease at 5 and 3 years after surgery, respectively.

Drug safety

A total of 453 polychemotherapy cycles were delivered to 82 patients. One subject refused therapy, five patients interrupted the therapy after the first cycle without any clinical evidence of PD, three patients were withdrawn by study because of early PD and one because of missing follow-up. Nine FDE cycles were administered to 22 patients, eight cycles to two patients, seven cycles to one patient, six cycles to 24 patients, five cycles to three patients, four cycles to one patient, three cycles to 18 patients, two cycles to five patients and one cycle to five patients.

Regarding the toxicity of intensified FDE chemotherapy, alopecia and neutropenia were the most frequent and the most severe (NCI CTC grade 3/4) adverse effects recorded. No patient was withdrawn from the study because of adverse effects and no patient was given growth factor for neutropenia. No treatment-related death occurred during FDE polychemotherapy. Table 5 reports the number and intensity of the toxicity episodes occurring during FDE treatment.

Discussion

The response rate (27.8% in the standard analysis) shown by the intensified-dose FDE regimen is higher than or comparable to that of other polychemotherapy regimens [17, 18, 30–32], with a high percentage of disease stabilisation lasting >6 months (45.8% in the standard analysis). The percentage of patients in which treatment was globally successful was close to 70%, with the highest percentages for foregut, midgut, unknown primary site NETs and MTCs.

It has already been demonstrated that NETs have a survival dependent on the histotype [33]. In our case series, after a 60 month follow-up TTP and OS are not significantly different in patients with gastroenteropancreatic NETs and lung carcinoids with respect to other NETs. This result is noteworthy, because intensified FDE was demonstrated to have similar efficacy in tumours characterized by both high and low aggressiveness. Because no standard therapy exists for NETs and our findings may be biased by the few figures of MTCs and Merkel's cell carcinomas, comparisons of our data on TTP and OS with those of previous studies must be cautious. However our experience may give useful information, as the FDE scheme was evaluated in a large population consisting of consecutive and unselected NET patients.

As regards the biochemical response, FDE treatment proved effective in inhibiting the inappropriate hormone release characterising some NETs. In 25% of patients with altered biomarker levels, FDE normalised the hormonal production. This has important clinical relevance because hormone release may be responsible for syndromes that can be life-threatening. FDE polychemotherapy induced biochemical responses lasting several months after the termination of therapy, as demonstrated by CgA evaluation during the follow-up of patients with or without tumour-related syndromes.

The intensified FDE regimen also displayed activity in controlling syndromes associated with carcinoids and MTCs: seven of 18 syndromic patients (38.9%) experienced a complete remission of the symptoms and 16.7% a partial subjective response.

The treatment was well tolerated; the most frequent adverse effects were NCI CTC grade 3/4 alopecia and, in a minor number of cases, neutropenia. In no case did the neutropenia require the administration of growth factors. Moreover, no febrile sepsis or treatment-related death occurred during treatment.

The FDE regimen proved to have also some activity as cytoreductive therapy. Six of eight patients were submitted to radical surgery and in two cases the patients were disease-free at 3 and 5 years post-surgery.

These data suggest that polychemotherapy including 5-FU, dacarbazine and epiadriamycin is safe and efficacious for the treatment of carcinoids and other less differentiated and more aggressive NETs (Merkel's cell carcinomas, MTC and pancreatic islet-cell tumours).

When our trial started the clinico-biological parameters usually considered by pathologists were not sufficient to clearly identify tumours having a worse prognosis. Nevertheless, our efforts were aimed at describing the clinical data by classifying patients according to the biological aggressivenes of the tumour. Because of the lack of important classification-related information, our subdivision of patients into different subgroups is largely unsatisfactory, although some findings would lead to the conclusion that a thorough NET patient selection may be useful at least to improve the objective response rate and TTP. The recent endocrine tumour histotyping proposed by the WHO [34] was prepared with the specific aim of studying these tumours in a multidisciplinary fashion. This new approach will prove very useful to clinicians in directing NET patients to more tailored therapies.

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