

## on of neuroendocrine tumours useful for selecting an appropriate treatment?

E. Bajetta<sup>1\*</sup>, L. Catena<sup>1</sup>, G. Procopio<sup>1</sup>, E. Bichisao<sup>2</sup>, L. Ferrari<sup>3</sup>, S. Della Torre<sup>1</sup>, S. De Dosso<sup>1</sup>,  
 S. Iacobelli<sup>4</sup>, R. Buzzoni<sup>1</sup>, L. Mariani<sup>5</sup> & J. Rosai<sup>6</sup>

<sup>1</sup>Medical Oncology Unit 2, <sup>2</sup>ITMO Group, <sup>3</sup>Nuclear Medicine, <sup>5</sup>Department of Statistics, <sup>6</sup>Department of Pathology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan; <sup>4</sup>Università degli Studi 'G. D'Annunzio', Chieti, Italy

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**Background:** Neuroendocrine tumours (NETs) are a rare and heterogeneous group of neoplasms. The most recent WHO classification provides clinical tools and indications to make the diagnosis and to suggest the correct treatment in different subgroups of patients. The aim of this trial was to apply the new classification criteria in clinical practice and, accordingly, to choose the most appropriate treatment.

**Patients and methods:** Thirty-one evaluable patients, not previously treated, classified as advanced well differentiated NETs according to the new classification, were given long-acting release octreotide 30 mg every 28 days until evidence of disease progression. The treatment activity was evaluated according to objective, biochemical and symptomatic responses. Safety and tolerability were also assessed.

**Results:** Two partial objective tumour responses were obtained (6%), stabilization occurred in 16 patients (52%) and 95% of patients had a disease stabilisation lasting  $\geq 6$  months. However, eight patients showed rapid disease progression within 6 months of therapy and six patients after 6 months. Biochemical responses, evaluated by changes in serum chromogranine A levels were reported in 20/24 patients (83%). Symptomatic responses were observed in 6/14 patients (43%): a complete syndrome remission in one patient, partial syndrome remission in five patients, no change in four patients and progressive disease in four patients. The median overall survival was not reached, and the median time to disease progression was 18 months (range 1–49 months). The treatment was well tolerated, no severe adverse events were observed and no patient withdrew from the study because of adverse events.

**Conclusions:** The WHO classification enables identification of low-grade NET patients who may be suitable for hormonal treatment. Octreotide LAR was seen to be effective in controlling the disease and was well tolerated. However, eight patients failed to respond to the treatment, despite histological evidence of a well differentiated tumour according to the new classification. This suggests that further histological examination should be carried out, especially in patients with visceral metastases and a short disease-free interval.

**Key words:** hormonal treatment, low-grade neuroendocrine tumours, WHO classification

biological characteristics: cellular grading, primary tumour size and site, cell proliferation markers, local or vascular invasiveness, and the production of biologically active substances. The main categories of tumour are classified as follows: well differentiated endocrine tumours characterised by a low grade of malignancy and well differentiated endocrine carcinomas which are more aggressive because of the presence of metastases; poorly differentiated endocrine carcinomas with a high grade of malignancy and a poor prognosis; mixed exocrine–endocrine tumours. This classification enables neuroendocrine tumours in the gastroenteropancreatic tract to be diagnosed easily, but unfortunately it is not applicable to lung tumours.

The classification of lung tumours is currently based on that of Travis et al. [6] who recognised the following categories: typical carcinoid, atypical carcinoid, small-cell lung cancer (SCLC) and large-cell neuroendocrine carcinoma (LCNC). Typical carcinoids have a clinical behaviour similar to that of well differentiated neuroendocrine tumours; SCLC and LCNC are poorly differentiated neuroendocrine carcinomas. Atypical carcinoids are found to be more aggressive than typical carcinoids but less aggressive than small-cell carcinoma (poorly differentiated NETs). Furthermore, a few moderately differentiated tumours with cellular and structural types intermediate between well and poorly differentiated NETs have also been found among gastroenteropancreatic NETs. This observation supports the comments in the introduction to the second edition of the *Histological Typing of Endocrine Tumours* by Solcia et al. [5] that this was not sufficient to warrant a separate category at these sites or in the general classification of endocrine tumours. However, the new WHO classification provides important clinical features which aid in formulating a diagnosis and a prognosis and, consequently, in suggesting suitable therapeutic programmes for NETs.

The poorly differentiated tumours together with SCLC and LCNC have a high proliferation index and can be treated with chemotherapy, although there is not yet a standard combination regimen. Cisplatin plus etoposide and streptozotocin in combination with 5-fluorouracil and doxorubicin are frequently employed [7, 8]. Recently a new combination chemotherapy with doxorubicin, 5-fluorouracil and dacarbazine has demonstrated its activity in the treatment of NETs [9].

be related to the reduction of tumour growth factors, such as insulin-like growth factor (IGF-I) and epidermal growth factor (EGF), and to the reduction of biologically active substances. On average, somatostatin analogues are able to achieve syndrome control and biochemical changes in 70% and 30–50% of patients, respectively, but they are associated with a very low rate of objective response (~10%) [17].

The use of long-acting (LAR) formulations of octreotide has provided a significant improvement in patient compliance by changing the schedule from three daily subcutaneous administrations to one intramuscular administration every 28 days [19].

In light of this evidence, we decided to select patients with low-grade NETs, who had never been treated, using the new WHO classification and, for the reasons mentioned above, to treat them with a somatostatin analogues, with the aim of evaluating the consistency between diagnosis and response rate.

## Patients and methods

### Patients

A total of 31 consecutive patients with metastatic or locally advanced well differentiated NETs, who had not previously been treated, entered the study between May 2000 and October 2002. The trial involved two centres and was co-ordinated by the Division of Medical Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy. Patient characteristics are summarised in Table 1.

The histological diagnosis of well differentiated NET was assessed in 30 patients using the new WHO criteria [5]; a diagnosis of medullary thyroid carcinoma (MTC) was obtained in only one patient. We treated this patient with somatostatin analogues because his clinical condition precluded the use of chemotherapy. Six patients presented with lung primary tumour and three of them had atypical carcinoid. The decision to include these patients in this study was based on the absence of a standard first-line treatment for these neoplasms. Only 12 patients received surgical intervention on the primary tumour; the other 19 patients presented with an inoperable tumours at diagnosis.

The following variables were recorded for each patient before starting treatment: sex, age, performance status (<2 ECOG), disease-free interval (DFI), number of metastatic sites, Octreoscan® uptake, bone radiographs, presence or absence of carcinoid syndrome and serum chromogranin A (CgA) and calcitonin (Ct) levels.

The study was approved by the local institutional ethical committee. The patients gave their informed written consent before starting the trial.

### Somatostatin analogue treatment

Treatment consisted of injection of LAR octreotide 30 mg intramuscularly

	6) yr
Male	23 (74%)
Female	8 (26%)
Performance status (ECOG)1	
0	27 (87%)
1	4 (13%)
Previous surgery	12
Median time between surgery and relapse	6 (2–36) months
Site of primary	
Pancreas	11 (35%)
Small bowel	6 (25%)
Lung	6 (20%)
Unknown	5 (17%)
Thyroid	1
Site of metastases	
1 site	13 (47%)
≥ 2 sites	16 (53%)
Local advanced disease	2
Metastatic disease	29 (93%)
Pathological levels of markers	
CgA	23 (74%)
Calcitonin	1
Carcinoid syndrome	
Present	14 (45%)
Absent	17 (55%)
Diarrhoea	11 (79%)
Flushing	6 (43%)
Cardiac syndrome	11
Abdominal pain	4 (29%)
Other	11

assessed every 3 months thereafter. The change in tumour size was calculated according to the WHO criteria [16]. The symptoms were monitored monthly in the first 3 months of treatment, and then every 3 months until the end of the study. The biochemical response was assessed by measuring serum CgA levels because this biomarker is the most useful indicator for NET monitoring [20–22]. The evaluation of serum Ct levels was also performed for the patient with diagnosis of MTC.

## Specimen collection and analytical methods

**Table 2.** Characteristics of eight patients with disease progression after 3–6 months of treatment

No. of patients	8/31 (25%)
Median age (range)	58 (28–66) years
Male/female	8/0
Performance status	
0	6
1	2
Previous surgery	2
Median time between surgery and relapse	2.2 months
Site of primary	
Lung	4
Pancreas	1
Thyroid	1
Unknown	2
Metastases and number of sites	
Liver only	3
Liver and peritoneum	1
Liver and mesentery	1
Liver and bone	1
Liver, lung and bone	1
Liver, lung, pancreas and bone	1
Pathological levels of markers	
CgA	5
5-HIAA	1
NSE	1
Calcitonin	1
MIB-1 <sup>a</sup>	
Pt 5	18%
Pt 9	2%
Pt 15	2%
Pt 19	3%
Pt 29	10%
Octreoscan <sup>®</sup>	
Positive	4
Negative	2
Unknown	2

<sup>a</sup>Could not be assessed in three patients.

## Statistical analysis

This was an open non-comparative clinical study in which no null hypothesis was being tested. The major endpoint was to evaluate the consistency between the diagnosis of low-grade NETs and the response rate in patients

disease had results of differentiated NET. The reasons for this failure in antitumour response were investigated and we concluded that further examination (e.g. proliferative index) would be necessary in order to confirm the histological diagnosis. On the basis of these conclusions, we decided to re-evaluate the histological samples from these patients in an attempt to identify variables of prognostic value. The histological re-examination of all samples was performed by a single pathologist, and the details are reported in the relevant sections.

### Tumour response

No complete responses occurred; two partial responses (6%) were observed and disease stabilisation occurred in 16 patients (52%). In 95% of patients disease stabilisation lasted for  $\geq 6$  months.

Thirteen patients (42%) showed a disease progression: eight patients (26%) had an early progression before 3–6 months of treatment, and six patients (19%) progressed after 9 months of treatment. Surgery was carried out in only two of these patients; in the remaining cases the disease was metastatic at diagnosis. It is worth noting that DFI (from surgery to disease relapse) was 2.2 months in the patients who experienced an early progression compared with 6.0 months for all the patients studied.

Table 2 summarises the characteristics of the eight patients with disease progression within 6 months. The pattern of clinical responses is in agreement with that observed in other trials [20, 21, 23], because eight patients (26%) were withdrawn from the treatment with LAR octreotide after only three to six administration (two patients after two administrations) because of rapid disease progression. After this treatment failure, these patients were treated with chemotherapy and they experienced prolonged disease control.

The histological analyses carried out after the study (Tables 2 and 3) failed to identify any reason for the failure of

the hormonal treatment. However, it is worth noting that in these patients the disease progression always occurred in liver with the involvement of other sites. The marker levels were pathological in all the patients; however, MIB-1 (assessable in six patients) was very high in only two patients, who had metastases in liver and peritoneum and in liver, lung and bone, respectively.

### Biochemical response

Serum CgA levels were evaluable in 24 patients, with an upper normal limit  $\leq 34$  U/l. At baseline, increased serum CgA levels were observed in 23/24 patients (96%), and after 3 months of treatment there was a decrease ( $>50\%$  compared with the baseline value) in 11/24 patients (46%). These patients showed the following clinical response: two complete responses (18%), three partial responses (27%), four no change (36%) and two disease progressions (19%). Serum CgA levels were assessable in only three patients with rapid disease progression, and dramatically increased compared with baseline values which were already out of normal range.

In the patient with diagnosis of medullary thyroid carcinoma, calcitonin was above the normal limit at baseline. The patient experienced an early progressive disease and the new value of the marker was not assessable.

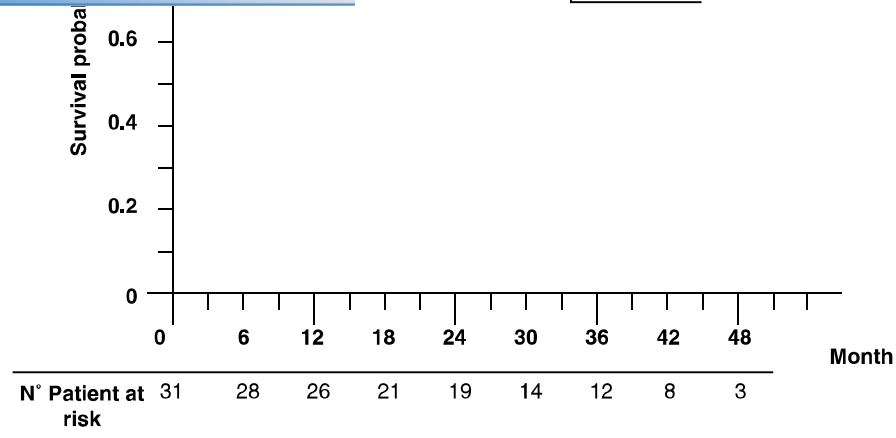
### Subjective response

The effects of LAR octreotide were evaluated in 14 patients (46%) with carcinoid syndromes. The syndrome disappeared completely in one patient, while a reduction of intensity or frequency of episodes (diarrhoea and flushing) occurred in five patients (35%). In four patients (28%) the symptoms did not change. Five patients experienced symptom progression. Three patients with early disease progression had carcinoid syndrome, but the reduction of symptoms was significant in only one patient.

### Overall survival and time to progression

The study was closed on 1 January 2003. The median overall survival was not reached and the median TTP was 18 months

**Table 3.** Characteristics of eight patients with disease progression according to MIB-1, octreoscan and markers



**Figure 1.** Overall survival.

(range 1–49 months). The OS and TTP curves are shown in Figures 1 and 2, respectively.

### Tolerability

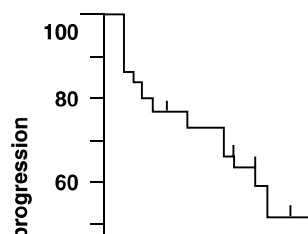
Diarrhoea (7%), steatorrhoea (17%) and abdominal pain (7%) were the most frequent grade 1–2 adverse effects recorded. No adverse NCI-CTC grade 4 events were recorded, and no patient was withdrawn from the study because of adverse effects.

### Discussion

The carcinoid tumours were described more than 100 years ago and considered to show indolent behaviour compared with typical adenocarcinomas [24]. It is well known that the

clinical diagnosis of NETs is uncertain, difficult and often occasional, resulting in NETs generally being considered as tumours of low incidence. The difficulty in identifying patients with NETs is compounded by the problem of NET classification and, as consequence, it is difficult to select the appropriate therapeutic approach.

Capella et al. [25] published a revised classification suggesting replacement of the term ‘carcinoid tumours’ by the term ‘neuroendocrine tumours’ to include all neuroendocrine tumours. This classification was updated by Solcia and colleagues and adopted by the WHO [5], who suggested the following categories: (1) well differentiated endocrine tumours characterised by a low grade of malignancy and well differentiated endocrine carcinomas which are more aggressive because of the presence of metastases; (2) poorly differentiated endocrine carcinomas; (3) mixed exocrine–endocrine





hormone therapy.

In agreement with these recommendations, the current trial was carried out on 31 evaluable patients showing histologically well differentiated NETs with a metastatic disease. All of these patients were treatment naive, a factor which accounts for the low number of recruited subjects. However, there was no bias due to any previous interference with tumour responses by pharmacological treatment.

Despite the confirmed presence of a low aggressive tumour, disease progressed rapidly in eight patients although they received the appropriate therapy. In order to explain these results we re-evaluated their histological samples, but unfortunately these tests were unable to suggest or discriminate any predictive value for expected clinical response and prognosis, because no correlation was found between MIB-1, mitotic count, grading, presence of necrosis and vascular and/or lymphatic invasion. These patients showed the clinical picture of the tumour with similar characteristics, because all of them had liver metastases and about 50% suffered from a primary lung tumour: thus a primary neoplasm of the lung and the presence of extensive liver metastatic disease could explain the poor response to therapy. The difference in DFI between non-responders and responders to the treatment is interesting (2.2 months compared with 6.0 months). However, this evidence was obtained from a small number of patients (two compared with 12 patients). Thus our experience suggests that, while the new classification is a useful tool for a preliminary selection of patients, it has limitations.

These data seem to be consistent with the observations of Travis et al. [6] about atypical NETs which can be identified as either well differentiated NETs or poorly differentiated NETs and, interestingly, not only for lung but also for gastroenteropancreatic tract tumours.

We would like to highlight the observation that responding patients, i.e. those with an appropriate diagnosis, showed prolonged overall survival. This result is consistent with the study by Quaedvlieg et al. [26] who showed an improved survival in patients with metastatic disease diagnosed after 1992, probably because of the use of somatostatin analogues. In our series the median survival time was not reached, whereas it was 43 months in unselected patients at any stage of

although the clinical and prognostic impact of each of these variables remains to be established.

We have in progress a clinical study that takes into account these suggestions, and further clinical trials are warranted.

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