9. Pharmacological therapy of neuroendocrine tumors

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Evolving perspectives on antiproliferative effects of octreotide treatment: the PROMID data

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Introduction

Somatostatin analogs are currently indicated for the relief of symptoms associated with hypersecretion syndromes in patients with gastroenteropancreatic neuroendocrine tumors (NETs). However, antiproliferative efficacy of somatostatin analogs is still debated.

In patients with metastatic well-differentiated neuroendocrine tumors (NETs), antiproliferative treatment is intended to reduce tumor burden, delay tumor progression and prolong survival. Available antiproliferative treatment options include surgical, ablative, radiotherapeutic, and pharmacological strategies, most of which are associated with adverse effects that can compromise quality of life. Somatostatin analogs are associated with minimal adverse effects. For this reason, they have been offered to patients with metastatic disease not amenable to surgery. However, the ability of somatostatin analogs to control tumor growth remains controversial. Antiproliferative effects have been reported in uncontrolled *in vivo* and *in vitro* studies[1,2], including early case reports where tumor shrinkage and even tumor disappearance were shown. In prior studies on antiproliferative effects of somatostatin analogs in NET patients, tumor stabilization was demonstrated in about half of the patients but only very few objective responses (≤5%) were observed[3-10]. Some limitations of these prior trials have to be taken into consideration: None of these studies was placebo controlled and limited number of patients (range, 15-50 patients) was included; most of them included a heterogeneous patient population presenting with NETs of different origin and biological behaviour. Furthermore, these studies did not include treatment-naïve patients and different dosages/formulations of somatostatin analogs were used. Given these considerations, one could argue that the observed disease stabilization may reflect the course of the disease rather than the effect of treatment. The PROMID study[11] was conducted to evaluate antiproliferative efficacy of 30 mg octreotide LAR in a well-defined population of patients with metastatic midgut neuroendocrine tumors (NETs). This paper provides an overview of the PROMID study and focuses on the results from the interim analysis that was pre-planned after the occurrence of 64 events.

Overview of the PROMID study

The PROMID study was a randomized, double-blind, placebo-controlled, phase IIIb trial conducted at 18 German academic centers. To avoid a heterogeneous population, only patients with well-differentiated midgut tumors were included. The main inclusion criteria were as follows: histologically confirmed, locally inoperable or metastatic well-differentiated midgut NET; primary tumor located in the midgut or unknown primary if a primary tumor outside the midgut was excluded; no curative therapeutic option available; measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) scan; functionally inactive or mild carcinoid syndrome, Karnofsky index >60; treatment-naïve patients (only previous surgical procedures were allowed, whereas patients previously treated with somatostatin analogs for ≥4 weeks or interferon alfa, chemotherapy or chemoembolization were excluded).

After collection of written informed consent from all participants and a screening phase to ascertain eligibility, eighty-five (85) patients from the planned 162 were randomized in a 1:1 ratio to receive octreotide LAR 30 mg intramuscularly or placebo (NaCl) every 28 days. Treatment was continued until CT- or MRI-documented tumor progression. CT and/or MRI scans were evaluated by a blinded central reader. The primary endpoint was time to tumor progression (TTP), defined as the time from randomization until the first evidence of progressive disease or tumor-related death. Secondary endpoints included survival time, defined as the time from randomization to tumor-related death, tumor response according to the World Health Organization (WHO) criteria, biochemical response, symptom control, quality of life and safety.

With regard to statistical analysis, an optimized group sequential design, with one interim analysis after observation of 64 events (progression or tumor-related death) and the final analysis after observation of 124 events, was fixed in the study protocol. Log-rank test was used to calculate time to progression, with a two-sided *P*-value of 0.0122 as defined by Lan-De Mets α-spending function indicating statistical significance. Survival curve estimation was performed using the Kaplan-

Meier method. Other statistical methods used included univariate and multivariate Cox regression models, Fisher's exact test and Wilcoxon-Mann-Whitney test.

Results

Time to progression

Of the 85 enrolled patients, 42 were assigned to receive octreotide LAR and 43 were randomly assigned to receive placebo. Patients characteristics were well balanced between the two arms (Table 1). Median age was slightly above 60 years and male and female patients were almost equally distributed in both groups. Karnofsky score was quite good in most patients and carcinoid syndrome was present in about 40% of patients in both groups. 66% of all patients had a primary resection prior to entering the study and hepatic tumor load was ≤10% in most cases. About 97% of patients had distant metastases and about 95% presented a Ki-67 value up to 2%, meaning a G1 tumor grade. The only slight imbalance was time since diagnosis, which was longer in the octreotide group compared to the placebo group (7.5 months and 3.3 months, respectively).

At the time of the planned interim analysis, 67 tumor progressions and 16 deaths were observed. Median time to tumor progression was 14.3 months in the octreotide

Table 1 - Baseline patient demographics and clinical characteristics

	Octreotide LAR (n = 42)	Placebo (n = 43)	Total (n = 85)
Median age, years*	63.5 [38,54,70,79]	61.0 [39,52,67,82]	62.0 [38,54,68,82]
Gender			
Male (%)	47.6%	53.5%	50.6%
Female (%)	52.4%	46.5%	49.4%
Time since diagnosis, months*	7.5 [0.8,3.5,19.8, 271.7]	3.3 [0.8,1.8,8.9, 109.4]	4.3 [0.8,2.5,14.3, 271.7]
Karnofsky score			
≤80	16.7%	11.6%	14.1%
>80	83.3%	88.4%	85.9%
Carcinoid syndrome	40.5%	37.2%	38.8%
Resection of primary	69.1%	62.8%	65.9%
Hepatic tumor load			
0%	16.7%	11.6%	14.1%
>0-≤10%	59.5%	62.8%	61.2%
>10-≤25%	7.1%	4.7%	5.9%
>25-≤50%	11.9%	9.3%	10.6%
>50%	4.8%	11.6%	8.2%
Distant metastases	97.6%	97.7%	97.7%
Ki-67 up to 2%	97.6%	93.0%	95.3%
CgA elevated	61.9%	69.8%	65.9%

*Median (minimum, 1st quartile, 3rd quartile, maximum).

LAR group and 6 months in the placebo group (hazard ratio [HR] = 0.34; 95% CI, 0.20-0.59; P = 0.000072; Figure 1). The intent-to-treat (ITT) analysis update for the American Society of Clinical Oncology (ASCO) presentation revealed only marginal changes for the primary endpoint, with median TTP of 15.6 and 5.9 months in the octreotide LAR and placebo groups, respectively (HR = 0.33; 95% CI, 0.19-0.55; P = 0.000017; Figure 2).
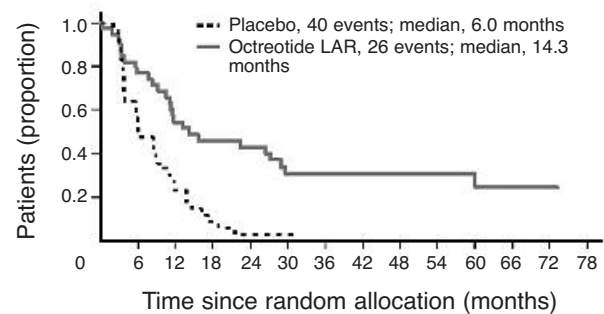
Treatment outcome was similar in patients with functionally active (HR = 0.23; 95% CI, 0.09-0.57) and inactive tumors (HR = 0.25; 95% CI, 0.10 to 0.59, per protocol analysis) and was not influenced by patients' age and chromogranin A levels. Conversely, the antiproliferative response was more pronounced in patients with hepatic tumor load ≤10% (HR = 0.21, 95% CI, 0.10-0.44; P <0.0001, per protocol analysis) and resected primary tumor.

Seven and nine deaths were observed in the octreotide LAR and placebo groups, respectively. The HR

No. of patients at risk
Placebo   43 21 9   3   1   1   0   0   0   0   0   0   0   0
Octreotide LAR 42 30 19 16 15 10 10 9   9   6   5   3   1   0

Log-rank test stratified by functional activity: P =.000072, HR 0 0.34 (95% CI, 0.20 to 0.59)

Figure 1 - Kaplan-Meier plot of time to progression or tumor-related death. ITT analysis.
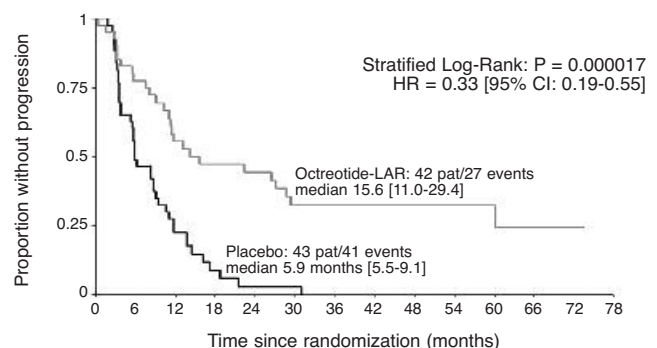

Figure 2 - Kaplan-Meier plot of time to progression or tumor-related death. ITT analysis ASCO update (follow-up until May 2009).

for overall survival was 0.81 (95% CI, 0.30 to 2.18). Because of the low number of deaths reported, median overall survival could not be estimated.

Morphological response according to WHO criteria

After six months of treatment, tumor progression rates were 23.8% in the otcreotide LAR group compared with 53.5% in the placebo group. Disease stabilization rates were 66.6% and 37.2% in the octreotide LAR and placebo groups, respectively. Only one partial response was observed in either group. No complete response occurred. Comparison by the Wilcoxon-Mann-Whitney test showed a significant difference in favour of otcreotide LAR (P = 0.0079; Table 2).

Table 2 - Morphological response after 6 months of treatment with otcreotide LAR or placebo. Wilcoxon-Mann-Whitney-test (P = 0.0079)

Response	Octreotide LAR		Placebo	
	n	%	n	%
	42		43	
Unknown	3	7.1	3	7.0
CR	0	0	0	0
PR	1	2.4	1	2.3
SD	28	66.6	16	37.2
PD	10	23.8	23	53.5

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; LAR, long-acting release.

Adverse events/safety

Observed safety findings were consistent with those reported in previous studies with otcreotide LAR in patients with NETs. Treatment-related deaths did not occur. Serious adverse events (AE) were reported in 11 patients treated with otcreotide LAR and in 10 patients treated with placebo. WHO grade 2 to 4 adverse events, regardless of causal relationship to treatment, occurred more often in the otcreotide LAR arm and included diarrhea, flatulence and bile stones. Treatment was discontinued because of AEs in 5 of 42 otcreotide LAR recipients and in 0 of 43 placebo recipients.

Conclusions

In this study, octreotide LAR significantly prolonged time to tumor progression in a well-defined population of patients with metastatic well-differentiated NETs of midgut origin. The most favourable effect was tumor stabilization, which was observed in 66.7% of octreotide LAR recipients compared with 37.2% of placebo recipients at six months. Considerably, treatment outcome was not influenced by tumor functional status. Patients

who benefited most from octreotide LAR treatment were those with a low hepatic tumor load and with the primary tumor resected. Whether or not octreotide LAR prolongs overall survival can not be answered. Further studies are needed to explore the impact of octreotide LAR on survival and to investigate its potential role in patients with NETs outside the midgut, in patients with G2 tumors, as well as in patients with few remaining metastases after cytoreductive surgery.

References

1. Shepherd JJ, Senator GB: Regression of liver metastases in patient with gastrin-secreting tumour treated with SMS 201-995. Lancet, 2: 574-576, 1986.
2. Susini C, Buscail L: Rationale for the use of somatostatin analogs as antitumor agents. Ann Oncol, 17: 1733-1742, 2006.
3. Saltz L, Trochanowski B, Buckley M, Heffernan B, Niedzwiecki D, Tao Y, Kelsen D: Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. Cancer, 72: 244-248, 1993.
4. Arnold R, Trautmann ME, Creutzfeldt W, Benning R, Benning M, Neuhaus C, Jürgensen R, Stein K, Schäfer H, Bruns C, Dennler HJ: Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. Gut, 38: 430-438, 1996.
5. Di Bartolomeo M, Bajetta E, Buzzoni R, Mariani L, Carnaghi C, Somma L, Zilembo N, di Leo A: Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the Italian Trials in Medical Oncology Group. Cancer, 77: 402-408, 1996.
6. Eriksson B, Renstrup J, Imam H, Oberg K: High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. Ann Oncol, 8: 1041-1044, 1997.
7. Ducreux M, Ruszniewski P, Chayvialle JA, Blumberg J, Cloarec D, Michel H, Raymond JM, Dupas JL, Gouerou H, Jian R, Genestin E, Hammel P, Rougier P: The antitumoral effect of the long-acting somatostatin analog lanreotide in neuroendocrine tumors. Am J Gastroenterol, 95: 3276-3281, 2000.
8. Aparicio T, Ducreux M, Baudin E, Sabourin JC, De Baere T, Mitry E, Schlumberger M, Rougier P: Antitumor activity of somatostatin analogues in progressive metastatic neuroendocrine tumours. Eur J Cancer, 37: 1014-1019, 2001.
9. Shojamanesh H, Gibril F, Louie A, Ojeaburu JV, Bashir S, Abou-Saif A, Jensen RT: Prospective study of the antitumor efficacy of long-term octreotide treatment in patients with progressive metastatic gastrinoma. Cancer, 94: 331-343, 2002.
10. Panzuto F, Di Fonzo M, Iannicelli E, Sciuto R, Maini CL, Capurso G, Milione M, Cattaruzza MS, Falconi M, David V, Ziparo V, Pederzoli P, Bordi C, Delle Fave G: Long-term clinical outcome of somatostatin analogues for treatment of progressive, metastatic, well-differentiated entero-pancreatic endocrine carcinoma. Ann Oncol, 17: 461-466, 2006.
11. Rinke A, Müller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, Mayer C, Aminossadati B, Pape U-F, Bläker M, Harder J, Arnold C, Gress T, Arnold R: Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. J Clin Oncol, 27: 4656-4663, 2009.

The role of chemotherapy in the treatment of neuroendocrine tumors

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Introduction

Neuroendocrine tumors (NETs) are highly heterogeneous neoplasms for which no standard treatment exists. Medical therapy is intended to improve quality of life, control symptoms due to hypersecretion of hormones and/or peptides, inhibit tumor cell proliferation and, possibly, prolong survival. During the so-called cytotoxic era, i.e. the 1960s and 1970s, chemotherapy has been the main treatment of disseminated neuroendocrine tumors (NETs). At that time, no other therapeutic modality was available. Over the subsequent decades, the development of new pharmacological therapies for NETs, such as biotherapies and targeted therapies, has considerably extended the therapeutic *armamentarium* for neuroendocrine disease. Nowadays somatostatin analogs are generally used for well-differentiated neuroendocrine carcinomas and functioning tumors, whereas chemotherapy is mainly reserved for rapidly growing disease which has progressed on less toxic treatments and poorly differentiated endocrine carcinomas. Several chemotherapeutic regimens have been evaluated, although not always with satisfactory results. However, many of the reports published in the literature are retrospective and/or involve small numbers of patients, which is mainly imputable to the relative rarity of NETs. Moreover, the assessment of the response to chemotherapy has been sometimes difficult, as these tumors exhibit long phases of spontaneous standstill, sudden explosive growth or even spontaneous regression. Over the years the assessment of the response to chemotherapy has significantly improved, and the increased knowledge on NETs has led to define different levels of response that must be taken into consideration when evaluating treatment, ie. objective response, biochemical response and symptomatic response. This paper provides an overview of the chemotherapeutic strategies which have been used for the management of NETs over the last five decades, and defines the role of chemotherapy in the current, multifaceted therapeutic landscape.

"Traditional" mono- and polychemoterapeutic regimens

The first experiences with chemotherapy in the treatment of NETs were conducted on very small series of patients and were based on the use of chemotherapeutic agents in monotherapy. In pancreatic NETs, objective response rates (ORR) from 41% to 17% were reported with streptozotocin (STZ), doxorubicin and clorozoticin monoterapies, with a duration of response not exceeding 16 months. Even more disappointing results were observed for intestinal NETs, in which mono-chemoterapies with doxorubicin (DOX), 5-fluorouracil (5-FU), dacarbazine (DTIC), STZ and cisplatin (CDDP) were associated with response rates up to 26% and a duration of response of about 5-6 months.

The first polychemotherapy regimens used for the treatment of metastatic NETs included mainly combinations of STZ with 5-FU or DOX, which in some cases were associated with a significant increase in response rates and duration. The best results were observed in patients treated with the combination STZ/DOX, in which an ORR of 69% and a duration of response of 27 months were reported. Various other chemotherapeutic regimens have also been employed, among which etoposide (VP16)/CDDP[1], 5-FU/DTIC/epiadriamycin[2], 5-FU/lomustine[3], FU/DOX and FU/STZ[4]. In general all these regimens, some of which were evaluated in trials on larger numbers of patients compared to previous studies, yielded moderate responses around 20%. The only exception was represented by anaplastic, poorly differentiated NETs, where short-term response rates of up to 67% were reported by Moertel *et al.* using the VP16/CDDP combination[1]. With particular regard to pancreatic NETs, the combinations STZ/adriamycin and STZ/5-FU produced tumor response rates of 69% and 45%, respectively, with quite satisfactory results in terms of response duration (18 and 14 months, respectively) and overall survival (2.2 and 1.4 years, respectively). Moreover, the DOX/STZ combination proved to be an efficient option for advanced well-differentiated pancreatic endocrine carcinomas, with an overall response rate of 36%, a median response duration of 19.7 months, and a median survival of 50.2% at 2 years and of 24.4% at 3 years[5]. The same and other schedules of polychemotherapy proved to be much less effective in intestinal NETs, where they yielded response and survival rates significantly lower compared with those achieved in pancreatic tumors.

As previously mentioned, Moertel *et al.* published in 1991 their experience with a regimen combining etoposide (VP16) and cisplatin (CDDP). More specifically, in this study the authors found a major therapeutic activity in the 18 patients with poorly differentiated NETs, with an objective response rate of 67% and a median duration of response of 8 months, whereas a significantly lower ORR of only 7% was observed in the 27 patients with well-differentiated NETs.[1] Since this publication, polychemotherapy with VP16 and platinum compounds has been considered as the reference treatment for inoperable poorly differentiated NETs, and has been further evaluated in retrospective confirmatory analyses. However, although poorly differentiated NETs were

found to be consistently chemosensitive to the etoposide plus cisplatin combination, their prognosis remained poor, with most of the patients relapsing quickly and reporting a 2-year survival lower than 20%[6].

New chemoterapeutic agents: capecitabine and oxaliplatin (XELOX)

More recently, capecitabine and oxaliplatin have become available and have found clinical application in the treatment of NETs. The combination of capecitabine and oxaliplatin (XELOX) has been assessed by Bajetta *et al.* in a phase II study on forty patients with advanced NETs[7]. Of these patients, 13 had previously untreated poorly differentiated NETs and 27 had well-differentiated NETs in progression after first-line therapy with somatostatin analogs. The XELOX regimen consisted of the intravenous administration of oxaliplatin 130 mg/m^2 on day 1 and the oral intake of capecitabine 2,000 mg/m^2/die from day 2 to day 15, every 3 weeks. Treatment was continued up to a maximum of 6 cycles, if feasible. The primary objective was the response rate including biochemical and symptomatic response; secondary objectives were time to progression (TTP) and safety. All the 40 patients were evaluated for response and toxicity. In the 13 patients with poorly differentiated NETs no complete response, 3 (23%) partial responses, 1 stabilization (7%) and 9 (70%) disease progressions were reported. In the low-grade population of 27 patients, 8 (30%) partial responses, 13 (48%) disease stabilizations and 6 (22%) disease progressions were observed. In this population, disease stabilization lasted 17 months (range, 3-39) and partial responses 12 months (range, 3-38; Table 1). In the low-grade population, for five lung NETs (typical and atypical carcinoids) there were three (60%) partial responses and one (20%) disease stabilization.

Among the 31 patients evaluated for serum chromogranin A (CgA) concentrations, 27 (87%) had increased CgA levels at baseline. After six chemotherapy cycles, there was a normalization of CgA levels in 1 patient, a decrease in 4 (14%) patients and stabilization in 2 (7%) patients. Patients with biochemical responses showed concordant tumour response. Symptomatic response was evaluated in 10 patients with carcinoid syndrome who continued treatment with somatostatin analogs during chemotherapy. Of these, five patients (50%) showed a complete disappearance of the syndrome, whereas four patients (40%) had a reduction of intensity or frequency of episodes. In the patients with low-grade tumors, median OS was 32 months and TTP was 20 months. The corresponding values for the patients with high-grade tumors were 5 months and 4 months, respectively, with a statistically significant difference in terms of OS in favour of the low-grade type (Figure 1).

These results demonstrated that the XELOX regimen can be an effective and tolerated treatment option for patients with well-differentiated NETs who have progressed after somatostatin analogs. Conversely, even though poorly differentiated NETs usually have a good response rate to regimens combining VP16 and platinum compounds, they show low sensitivity to the oxaliplatin and capecitabine association.

Combinations of chemotherapy and α-interferon

Regimens combining chemotherapeutic agents with interferon-α have been assessed with unsatisfactory results. Several studies on limited series evaluated the use of 5-FU and alpha interferon (α-IFN) based on reports of modest activity for both agents in NETs and on reports of enhanced activity for the combination of these

Table 1 - Objective responses observed in patients with high-grade and low-grade NETs after treatment with XELOX

Hystological type	Total patients (n)	CR	PR	SD	DP
High grade	13	-	3 (23%)	1	9 (70%)
Lung	5	-	2	1	2
Low-grade	27	-	8 (30%)	13 (48%)	6 (22%)
Lung	5	-	3	2	1
Total	40	-	11 (27.5%)	14 (35%)	15 (37.5%)

CR, complete response; PR, partial response; SD, stabilization of disease; PD, disease progression[7].
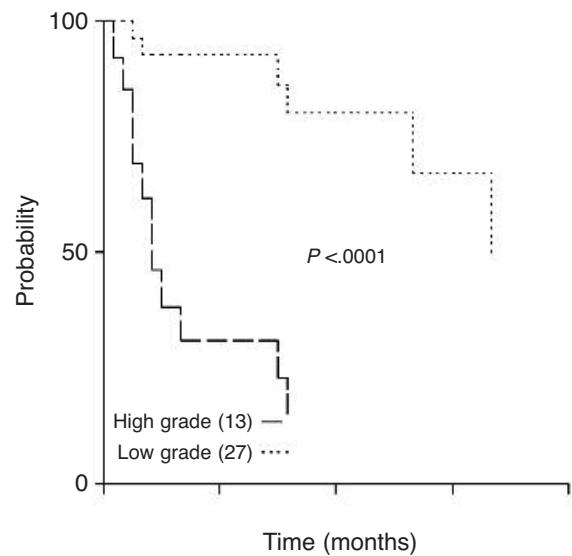

Figure 1 - Overall survival according to the histological type[7].

agents in other gastrointestinal malignancies. Results indicated that this combination was disappointing both in terms of tolerance and response rate. In fact, it did not show any clear superiority over the individual agents alone and was associated with considerable toxicity[8,9]. Similar results were observed for the combination of α-IFN with STZ and DOXO[10].

Conclusions

In well-differentiated NETs with low proliferation rate, mainly midgut carcinoids, chemotherapy is associated with low response rates and a short duration of response. Therefore, chemotherapy is not considered the first-line treatment for these patients and can be taken into account only after progression following other therapeutic strategies.

In poorly differentiated NETs with high proliferative index, mainly pancreatic NETs and foregut carcinoids, chemotherapy provides high response rates and a response duration higher than 18 months, and is therefore considered a first-line treatment. Possible chemotherapeutic combinations include STZ/5-FU and VP16/CDDP.

References

1. Moertel CG, Kvols LK, O'Connell MJ, Rubin J: Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Cancer, 68: 227-232, 1991.
2. Bajetta E, Ferrari L, Procopio G, Catena L, Ferrario E, Martinetti A, Di Bartolomeo M, Buzzoni R, Celio L, Vitali M, Beretta E, Seregni E, Bombardieri E: Efficacy of a chemotherapy combination for the treatment of metastatic neuroendocrine tumors. Ann Oncol, 13: 614-621, 2002.
3. Kaltsas GA, Mukherjee JJ, Isidori A, Kola B, Plowman PN, Monson JP, Grossman AB, Besser GM: Treament of advanced neuroendocrine tumors using combination chemotherapy with lomustine and 5-fluorouracil. Clin Endocrinol, 57: 169-183, 2002.
4. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG: Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol, 23: 4897-4904, 2005.
5. Delaunoit Th, Ducreux M, Boige V, Dromain C, Sabourin J-C, Duvillard P, Schlumberger M, de Baere T, Rougier P, Ruffie P, Elias D, Lasser P, Baudin E: The doxorubicin-streptozotocin combination for the treatment of advanced well-differentiated pancreatic endocrine carcinoma: a judicious option? Eur J Cancer, 40: 515-520, 2004.
6. Mitry E, Baudin E, Ducreux M, Sabourin J-C, Rufié P, Aparicio T, Lasser P, Elias D, Duvillard P, Schlumberger M, Rougier P: Treatment of poorly differentiated neuroendocrine tumors with etoposide and cisplatin. Br J Cancer, 81 (8): 1351-1355, 1999.
7. Bajetta E, Catena L, Procopio G, De Dosso S, Bichisao E, Ferrari L, Martinetti A, Platania M, Verzoni E, Formisano B, Bajetta R: Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumors? Cancer Chemother Pharmacol, 59: 637-642, 2007.
8. Saltz L, Kemeny N, Schwartz G, Kelsen D: A phase II trial of alpha-interferon and 5-fluorouracil in patients with advanced carcinoid and islet cell tumors. Cancer, 74: 958-961, 1994.
9. Hughes MJ, Kerr DJ, Cassidy J, Soukop M, MCGregor K, Blackburn N, Yosef H, Kaye SB: A pilot study of combination therapy with interferon-α-2a and 5-fluorouracil in metastatic carcinoid and malignant endocrine pancreatic tumors. Ann Oncol, 7: 208-210, 1996.
10. Janson ET, Ronnblom L, Ahlstrom H, Grander D, Alm G, Einhorn S, Oberg K: Treatment with alpha-interferon versus alpha-interferon in combination with streptozocin and doxorubicin in patients with malignant carcinoid tumors: a randomized trial. Ann Oncol, 3: 635-638, 1992.

Proposal of a treatment algorithm for the management of gastroenteropancreatic neuroendocrine tumors

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Introduction

Neuroendocrine tumors (NETs) of the gastroenteropancreatic (GEP) tract are a group of clinically and pathologically heterogeneous neoplasms. Most of them exhibit a slow growth, while others display highly aggressive behaviour with rapidly progressing malignant disease. The presenting features of NETs are typically vague and unspecific, but eventually most patients develop severe, life-threatening symptoms because of excessive hormone production from the tumor. From the clinical point of view, NETs are considered "functioning" when their secreted products produce symptoms such as flushing and diarrhea, and they are considered "nonfunctioning" when hypersecretory symptoms are absent.

In spite of significant advances in diagnostic techniques, NET patients typically experience long delays in diagnosis[1], and the majority of them are correctly diagnosed only at an advanced stage, when life-threatening clinical symptoms have been developed and the disease has already metastasized. Nonfunctioning tumors, in particular, are less likely to be detected unless found incidentally or when the primary or metastatic lesions have grown large enough to cause mass effects (e.g., bowel or biliary duct obstruction)[2]. In contrast, functioning tumors may be diagnosed earlier because of the dramatic and specific manifestations of endocrine hyperfunction, and may even be recognized when the primary lesion is less than 1 cm in diameter. In the case of

small bowel NETs, which are the most common NETs of the GEP tract, however, the onset of symptoms is usually indicative of hepatic metastasis[3].

Because of the heterogeneity of NETs in terms of clinical presentation and behaviour, the management and treatment of these neoplasms represents an engaging challenge to the clinician and requires an high level of expertise for diagnosis, pathology, cytoreductive or curative surgery, oncology, interventional radiology and nuclear medicine. No specific antineoplastic therapy is currently available, and most patients cannot have access to the multidisciplinary care necessary for an optimal management of these tumors. Moreover, since NETs are quite rare neoplasms, the number of patients annually seen at most individual centers is rather scarce, which highly limits the possibility to perform adequate studies and systematically assess new treatments. Given the paucity of sufficiently powered randomized, controlled, phase III clinical trials with homogenous and large patient populations and adequate follow-up in this field, making the right treatment choice is difficult and therapeutic decision-making must often rely on single-institution experiences on limited series. Current therapeutic approaches include biotherapy (α-interferons and somatostatin analogs) to control the symptoms associated with hormone hyperproduction; systemic chemotherapic regimens for advanced disease; surgery with curative intent (at the moment the only available option that can offer a cure) or palliative cytoreductive surgery; receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogs for inoperable or metastatic disease; and tumor ablation by radiofrequency or chemoembolization to reduce metastatic tumor bulk.

Surgery remains the treatment of choice for localized GEP NETs, and so far represents the only curative option for these patients. Unfortunately, in most patients surgery cannot be curative because of metastatic spread at the time of diagnosis. However, surgery can still have an important role also in patients with metastatic disease, especially for liver metastases. In particular, cytoreductive surgery, including resection of regional or distant metastases, radiofrequency ablation (RF) and cryotherapy, aims at improving symptoms by the control of peptide/amine excess, at improving quality of life and, possibly, at extending survival. When R0 resection is feasible, resection of metastasis is a potential curative option. Liver transplantation can be considered in selected cases, i.e., young patients without documented spread outside the liver and resected primary tumor[4].

Specific chemoterapeutic treatment, *i.e.,* streptozotocin (STZ), has been available since the 1960s. STZ has been used especially in combination with other cytotoxic agents such as 5-fluorouracil (5-FU) or doxorubicin, but has been of limited value for the treatment of well-differentiated GEP-NETs, such as the typical midgut carcinoids, with response rates around 10%-15%. Conversely, chemotherapy with cisplatin and etoposide has been the standard of care for malignant, poorly differentiated NETs, achieving response rates of 30%-50%[4]. The main indication of chemotherapy is the treatment of inoperable, poorly differentiated NETs[4,5].

Biotherapy for NETs consists mainly in somatostatin analogues and α-interferons. The main indication of somatostatin analogs is the treatment of functioning NETs causing hormone-related clinical syndromes, while their use in non-functioning NETs is still controversial, but this use is strongly suggested by PROMID study data[6]. Currently, the somatostatin analogs octreotide and lanreotide are the first line treatment of well differentiated NETs, in which they have proved effective in the control of symptoms and may also obtain disease stabilization. In particular, patients who benefit from treatment with somatostatin analogs include those with functional NETs of foregut and midgut origin. Selection of patients is based on a positive OctreoScan®[4,7]. Since the lack of cross resistance between octreotide and lanreotide has been demonstrated, patients on therapy with a somatostatin analog for more than 1 year who stop responding to treatment can be switched from octreotide to lanreotide and *vice versa*, without negative effects on therapeutic efficacy[7,8]. Alpha interferon (α-IFN) has been used for more than 20 years in the treatment of mid-gut NETs, with symptomatic and biochemical responses in 50% of patients and tumor reduction in 10-15%. A combination of somatostatin analogues and α-interferons has been effective in patients with resistance to either drug[4,7].

Peptide receptor radiotherapy (PRRT) can be dispensed as second-line therapy to patients who display high-grade uptake on somatostatin receptor scintigraphy.

Given the great biological and clinical diversity of GEP NETs, the treatment of these tumors is becoming more and more type-specific, and the design of a therapeutic algorithm that could encompass all GEP NET subtypes and conciliate the diverse opinions of all the international leading experts in this field would be hardly conceivable. Rather, the concept of a treatment algorithm can find some practical application with reference to particular segments or aspects of this complex and multifaceted disease. The present paper provides an attempt to develop a therapeutic algorithm for the management of the well differentiated neuroendocrine carcinoma (WDEC), which represents one of the GEP NET subtypes most frequently encountered in the clinical practice. The proposed algorithm is based on the WHO classification and the ENETS guidelines for treatment of GEP-NETs on one hand, and of the experiences performed at our institution on the other.

Basic principles that should guide the design of a treatment algorithm for GEP NETs

The development of a treatment algorithm should be based on a standardized diagnostic procedure which

takes into account several parameters, including mainly the primary site, the tumor differentiation and proliferative activity, the extension of disease, and the presence or absence of the carcinoid syndrome. Currently, the World Health Organization (WHO) classification and the European Neuroendocrine Tumor Society (ENETS) guidelines for the treatment of GEP-NETs represent the best available resources to make a correct recognition and prognostic stratification of the individual GEP NETs, in the attempt to offer an adequate treatment.

Once the neuroendocrine nature of the disease has been confirmed, the tumor should be categorized as well-differentiated endocrine tumour (WDET), well-differentiated endocrine carcinoma (WDEC), or poorly differentiated endocrine carcinoma (PDEC) according to the WHO classification of 2000[9]. At this point, its proliferative activity should be determined by counting the mitoses per high-power field and/or by immunostaining for the cell cycle-dependent marker Ki67 (MIB1) antigen. The value of the Ki67 labeling index provides important prognostic information and serves as the basis for the grading of the tumor as G1 (<2%), G2 (>2-20%) or G3 (>20%), according to the ENETS grading proposal for GEP NETs. Further information on the size of the tumor, its composition (presence of necrosis or cystic changes), its relationship to anatomic structures, resection margins and adjacent organs, as well as the presence of lymph node and other metastases, should be collected to assess the extension of the disease according to the ENETS TNM staging proposal[10,11].

The last factor that should be taken into consideration for the design of a treatment algorithm is the presence or absence of the carcinoid syndrome. The carcinoid syndrome is a combination of symptoms caused by the release of hormones into the bloodstream, and is present in about 30% of well differentiated NETs of the small intestine (midgut carcinoids)[4]. The symptoms associated with carcinoid syndrome in its typical form may vary depending on which hormones are released by the tumors, and generally include flushing, diarrhea, wheezing due to bronchospasm and endocardial fibrosis. Another less delineated form of the syndrome, namely the atypical carcinoid syndrome, may be encountered in 5-10% of patients with sporadic forms of gastric carcinoids, and less frequently in patients with poorly differentiated gastric NETs. The syndrome consists of patchy, intensely red flush, sweating, itching, sometimes also cutaneous oedema, bronchoconstriction, salivary gland swelling and lacrimation. It is usually associated with the presence of liver metastases and is due to the release of histamine and serotonin[12].

Patients with carcinoid syndrome undergoing surgery, endoscopic procedure, arterial embolization or other types of intervention are at risk of developing a severe, potentially fatal complication known as carcinoid crisis. The carcinoid crisis may be provoked by induction of anaesthesia during washing of the abdomen, or

as a result of tumor manipulation or tumor necrosis during surgery or intervention. It is characterized by sudden changes in blood pressure, most often hypotension, sometimes with concomitant onset of prolonged and excessive flushing, hyperthermia, and occasionally severe bronchospasm. Some patients have attacks of hypertension and even hypertensive crisis, due to the release of catecholamines by the tumor. Carcinoid crisis can result in death. Rapid reversal of this condition has been referred with the acute intravenous administration of octreotide. However, octreotide prophylaxis is highly recommended before surgery to prevent mediator release and the development of the crisis[12].

Proposal of a therapeutic algorithm for the treatment of GEP NETs

When the primary site is known and the tumor is resectable, the first line treatment of WDEC should be surgery. Once the primary tumor has been removed and if metastatic spread is limited to the liver, the patient should be evaluated for radical resection of metastases or for liver transplantation. If hepatic metastases are not resectable or in presence of extrahepatic dissemination, octreotide and lanreotide should be administered until progression of disease, followed by chemotherapy/PRRT or by the enrolment in a clinical trial with an experimental therapy in patients progressing after less than 1 year of therapy with somatostatin analogs, or by the cross-over to octreotide or lanreotide in patients who have received somatostatin analog therapy for more than 1 year but then stopped responding to treatment. Patients who progress on chemotherapy or PRRT should be given supportive therapy.

In a situation of unknown primary, lanreotide or octreotide should be administered until progression of disease, followed by chemotherapy/PRRT or by the enrolment in a clinical trial with an experimental therapy in patients progressing after less than 1 year from the start of therapy with somatostatin analogs, or by the cross-over to octreotide or lanreotide in patients no longer responding to octreotide or lanreotide after more than 1 year of therapy. Patients who progress on chemotherapy or PRRT should receive supportive therapy.

Conclusions

Gastroenteropancreatic neuroendocrine tumors are highly complex and heterogeneous neoplasms. Their management continues to represent a challenge even for the most skilled clinician, requiring an high degree of expertise in several medical and surgical fields. Therefore, the choice of therapy for GEP NETs must be accurately pondered, and should be highly individualized on the basis of current symptoms, tumor type and

burden, and additional prognostic information. Surgery remains the mainstay of treatment for localized disease, and currently is the only potentially curative option. Somatostatin analogs represent the therapy of choice for functioning well differentiated forms, and can effectively achieve the control of symptoms associated with hormone hypersecretion and release. Chemotherapy is instead reserved to poorly differentiated neuroendocrine carcinomas. However, its efficacy in achieving symptomatic control is of limited value.

Well differentiated neuroendocrine carcinoma (WDEC) represents one of the GEP NET subtypes most frequently encountered in the clinical practice. When primary localization is known and the tumor is resectable, the first line treatment of WDEC should be surgery. Second line therapy includes radical resection of hepatic metastases or hepatic transplantation in patients with metastastic spread limited to the liver, or treatment with somatostatin analogs in patients with unresectable hepatic disease or extrahepatic metastases. Chemotherapy, PRRT, or the cross-over to octreotide or lanreotide should be considered at time of progression. In a situation of unknown primary, lanreotide or octreotide should be administered until progression of disease, followed by chemotherapy, PRRT, or the cross-over to octreotide or lanreotide.

References

1. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD: Current status of gastrointestinal carcinoids. Gastroenterology, 128: 1717-1751, 2005.
2. de Herder WW: Tumours of the midgut (jejunum, ileum and ascending colon, including carcinoid syndrome). Best Pract Res Clin Gastroenterol, 19: 705-715, 2005.
3. Öberg K, Eriksson B: Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol, 19: 753-781, 2005.
4. Öberg K, Åkerström, G. Rindi G, Jelic S: On behalf of the ESMO Guidelines Working Group. Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 21: v223-v227, 2010.
5. Eriksson B, Annibale B, Bajetta E, Mitry E, Pavel M, Platania M, Salazar R, Plöckinger U, and all other Mallorca Consensus Conference participants: ENETS consensus guidelines for the standards of care in neuroendocrine tumors: chemotherapy in patients with neuroendocrine tumors. Neuroendocrinology, 90: 214-219, 2009.
6. Rinke A, Müller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, Mayer C, Aminossadati B, Pape U-F, Bläker M, Harder J, Arnold C, Gress T, Arnold R: Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. J Clin Oncol, 27 (28): 4656-4663, 2009.
7. Öberg K, Kvols L, Caplin M, Delle Fave G, de Herder W, Rindi G, Ruszniewski P, Woltering EA, Wiedenmann B: Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol, 15: 966-973, 2004.
8. Ricci S, Antonuzzo A, Galli L, Ferdeghini M, Bodei L, Orlandini C, Conte PF: Octreotide acetate long-acting release in patients with metastatic neuroendocrine tumors pretreated with lanreotide. Ann Oncol, 11: 1127-1130, 2000.
9. Solcia E, Klöppel G, Sobin LH: Histological typing of endocrine tumours, ed 2. WHO International Histological Classification of Tumours. Berlin, Springer, 2000.
10. Rindi G, Klöppel G, Ahlman H: TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch, 449: 395-401, 2006.
11. Rindi G, Klöppel G, Couvelard A: TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch, 451: 757-762, 2007.
12. Akerström G, Falconi M, Kianmanesh R, Ruszniewski P, Plöckinger U, and all other Mallorca Consensus Conference participants: ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre- and Perioperative Therapy in Patients with Neuroendocrine Tumors. Neuroendocrinology, 90: 203-208, 2009.

Thoracic and gastrointestinal neuroendocrine tumors: is it time for adjuvant treatment?

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Introduction

The aim of adjuvant treatment is to prevent metastatic disease after radical surgery. The effective benefit of adjuvant approach in thoracic and gastrointestinal neuroendocrine tumors (NETs) is still highly controversial and should be assessed in a large clinical trial. However, the possibility to perform such a trial represent a challenge, being hampered by several restrictions mainly correlated to the relative rarity of these tumors as well as by the extreme variability of their biologic and clinical behaviour. The effective benefit of adjuvant approach in thoracic and gastrointestinal neuroendocrine tumors (NETs) is still under debate and should be assessed in a large clinical trial. While trying to consider eventual adjuvant treatment for NET patients, there are first some unsolved questions to be answered, namely who are the patients that are candidates for adjuvant approach, and how feasible it is to find a large cohort for such rare tumors to reach high evidence level for recommendations?

The actual status of adjuvant approach for neuroendocrine tumors

Thoracic and gastrointestinal neuroendocrine tumors (NETs) are regarded as quite rare neoplasms. The esti-

mated incidence is about 3/100,000 per year (3000/100,000.000 per year) for the NETs arising from the gastrointestinal (GI) tract and 0.6/100,000 per year (600/100,000.000 per year) for NETs originating from the bronchopulmonary system[1,2]. It means that, although their incidence is low, there could be a theoretical possibility of gathering enough cases in a few years for an international trial covering several larger countries. The effective numbers of NETs reported in clinical series and single-institutions or international registries are however very low. Soga *et al.*[3] reported 11.842 cases for a period over 60 years emanating from 67 countries, 64% with primary localization in the digestive system, thus reflecting an overall incidence of 125 patients per year, i.e., 2 patients per year per country. About half of them was metastatic at diagnosis, a fact that decreases the number to 1 non metastatic patient per country per year. In a registry covering more recent years[4], neuroendocrine carcinomas had a median incidence of 11 cases per year, with the incidence sharply rising above this number in the last 20 years. Liu *et al.*[5] reported 26 gastric neuroendocrine carcinomas from 1964 to 2005, which amount to 3 cases every two years. Regional lymph node metastases only at diagnosis occurred in 12 patients, that would make 12 candidates for adjuvant treatment in 40 years in a single institution. Furthermore, in non-Asiatic data Khaled *et al.*[6] reported 150 patients with gastrointestinal neuroendocrine carcinomas at the Massachusetts general hospital for a 21 year period, that makes an incidence of 7 new patients per year. However, 22% had synchronous "non carcinoid" tumors and a significant percentage of residual patients developed metachronous "non carcinoid" tumors, a fact that would compromise results of any adjuvant approach. These data seem rather disappointing, and suggest initial restrictions for conducting a classical prospective controlled clinical trial that would provide level IA evidence data, related to low number of yearly cases both in high volume institutions and registries. However, in the recent years an increasing number of NET cases are better diagnosed, probably as a result of the significant advances in immunochemistry and in diagnostic techniques in general, and within a cooperative international group there could be an adequate number of patients that could be gathered and possibly enrolled into a large clinical trial.

In classical carcinomas of the digestive system adjuvant treatment do not have the same effectiveness for every localization, showing a moderate benefit for colon cancer, a moderate benefit for rectal cancer, which is increased by associated radiotherapy, doubtful if any benefit for gastric cancer and unknown benefit for jejunoileal cancer. By analogy with classical carcinomas, candidates to adjuvant approach should be patients with lymph node metastases only. However, this might not be the right approach: primary localization, histology and histologic grade, as well as the size of the primary tumor, may also be of utmost importance due to data related to impact on survival. Tumors arising from different districts of the GI tract may not have the same metastatic potential, as suggested by the rates of metastases at diagnosis of 15.1% for the rectum, 15.5% for the stomach, 12.5% for the duodenum and 37.2% for the jejunoileum[7]. Therefore, they should be assessed separately. Furthermore, not only large masses, but also small tumors below 1 cm or 0.5 cm of size should be included in a controlled trial because they have metastatic potential as well, as demonstrated by metastases rates of 9.7%, 7.9%, 10.5% and 30.2% for rectal, gastric, duodenal, and jejunoileal tumors below 1 cm, respectively, and of 3.7%, 4.6%, 8.3% and 17.2% for the corresponding localizations below 0.5 cm[7].

Based on available 5-years survival data, GI NETs without metastases at presentation generally fare very well after surgery even if they are not given adjuvant treatment, with 96.9% of patients still alive after 5 years from surgical intervention. Of course, patients with metastases at presentation behave rather worse, with 5-year survival rates lowering down to 64.7%. However, if survival of patients without metastases at presentation is so good, how can we calculate the benefit of adjuvant therapy for the whole group of patients?

Another open question is what chemotherapy to use in the adjuvant setting based on data from metastatic disease. A number of chemotherapeutic combinations have been evaluated in several phase II studies[8-11] and in a few phase III studies as well, but so far none of these regimen has proved to be very effective, and response rates in metastatic disease tend to be moderate or low. For instance in three studies with streptozotocin and 5FU response rate were 33%, 22% and 16%. Two studies investigated different doublets. The combination of 5FU and cyclophosphamide achieved a response rate of 26% in 47 patients and the combination of 5FU and doxorubicin resulted in a response rate of only 16% in 25 patients. A triplet combining strepozotocin, 5FU and cyclophosphamide was investigated in one study with a response rate 22%. A more aggressive regimen combining streptozotocin, doxorubicin, 5FU and cyclophosphamide yielded a response rate of 31%, not different for doublet chemotherapies.

Per analogy, 5-fluorouracil (5-FU) has a very moderate activity in classical digestive tract cancers. The combination of 5-FU and leucovorin (LV) provides a benefit for colon cancer patients, whereas its benefit is less clear for patients with gastric or pancreatic carcinomas. According to the metastatic potential, the category of GI NETs most likely to benefit from adjuvant treatment may be jejunoileal tumors. In effect, about one third of patients with jejunoileal tumors metastasize, with rate of metastases at diagnosis of 17.2% for tumors below 0.5 cm and 37.2% for tumors of more than 0.5 cm in size. However, jejunoileal tumors are among the less sensitive, with response rates to chemotherapy below 15%.

The data on adjuvant approach in the present literature are scarce and do not allow to draw any conclusion because they are derived from too small series. For instance, Liu et al.[5] reported that adjuvant chemotherapy showed no survival benefit in gastric neuroendocrine carcinomas, but one could argue if this datum can be taken for granted in a study involving 10/26 cases. Again, the number of patients is too small to assess the benefit of adjuvant treatment for patients having a good survival after 1, 2, 3, or 4 years, and an adequate evaluation should be made on a large cohort including several hundred patients. Of course, chemotherapy is not the only modality that can be used in the adjuvant setting. Somatostatin receptor-targeted radionuclide therapy has been also occasionally employed, but again in very small number of patients or even in single patients, and significant conclusions cannot be drawn.

Furthermore, to add to the confusion, we could mention that some small cell NETs from extra gastrointestinal and extra pulmonary localizations, such as those arising from the cervix uteri, the larynx or the head and neck region, have won their right to have an adjuvant treatment without any previous prospective controlled trial. The approach is the same as for classical cancers occurring in the same localization. If they are operable, these patients are operated, postoperatively irradiated and sometimes given an adjuvant chemotherapy, despite the fact that no trial demonstrated the benefit of such an intervention. In these cases, the introduction of adjuvant chemotherapy into the clinical practice has been guided not by clinical trials, but by clinical necessities.

Therefore, in the absence of well-established activity for chemotherapy in this disease there is no rationale to support the use of adjuvant chemotherapy.

Some more advanced data are available for pulmonary NETs. Nowdays it is widely recognized that small cell lung cancer (SCLC), being a systemic disease, is not amenable to surgery and therefore to adjuvant chemotherapy. As far as large cell neuroendocrine carcinoma (LCNEC) is concerned, retrospective data indicate some benefit of adjuvant approach. For instance, Hage et al.[12] showed a survival advantage in patient treated with surgery plus adjuvant chemotherapy (STZ/5-FU and ADM + CPM + VP-16) compared to surgery alone. Probably, also this therapeutic strategy was guided by clinical necessity, because LCNEC has the worst survival among pulmonary large cell cancers[13]. Other data demonstrated no survival benefit from non platinum-based regimes, but a clear survival extension with platinum-based ones in the adjuvant setting[14].

Conclusion

More or less clearly, there could be no illusion on the possibility of performing a large breast cancer-type adjuvant trial for neuroendocrine tumors and for achiev-

ing an evidence level IA recommendation. The aggressive potential of neuroendocrine carcinomas arising from particular sites and/or with particular histology asks at least for selected subgroups at risk, for directions concerning adjuvant approach and the choice of chemotherapy regimens. And we should not forget that clinical practice often goes ahead of results of clinical trials, especially when it is not possible to provide consensus statements due to scarcity of data. Of course, the idea of a decent trial should not be abandoned notwithstanding the level of evidence it could reach.

References

1. Oberg K, Jelic S: Neuroendocrine gastroenteropancreatic tumors: ESMO Clinical Recommendation for diagnosis, treatment and follow-up. Ann Oncol, 20 (Suppl 4), 150-153, 2009.
2. Oberg K, Jelic S: Neuroendocrine bronchial and thymic tumors: ESMO Clinical Recommendation for diagnosis, treatment and follow-up, Ann Oncol, 20 (Suppl 4), 147-149, 2009.
3. Soga J: Carcinoids and their variant endocrinocarcinomas. An analysis of 11842 reported cases. J Exp Clin Cancer Res, 22: 517-530, 2003.
4. Modlin IM, Lye KD, Kidd M: A 5-decade analysis of 13715 carcinoid tumors. Cancer, 97 (4): 934-959, 2008.
5. Liu Y, Liang H, Liu N, Zhang RP, Cui QH: Relationship of biological behavior and the prognosis in gastric carcinoid. Zhonghua Wei Chang Wai Ke Za Zhi, 10 (5): 472-475, 2007.
6. Khaled O, Shebani MD, Wiley W, Souba MD, Dianne M, Finkelstein D, Stark PC, Elgadi KM, Tanabe KK, Ott MJ: Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. Ann Surg, 229 (6): 815-830, 1999.
7. Soga J: Early-stage carcinoids of the gastrointestinal tract. An analysis of 1914 reported cases. Cancer, 103 (8): 1587-1595, 2005.
8. Moertel CG, Hanley JA: Combination chemotherapy trials in metastatic carcinoid tumor and the malignant carcinoid syndrome. Cancer Clin Trials, 2 (4): 327-334, 1979.
9. Engstrom PF, Lavin PT, Moertel CG, Folsch E, Douglass HO Jr: Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. J Clin Oncol, 2 (11): 1255-1259, 1984.
10. Bukowski RM, Johnson KG, Peterson RF, Stephens RL, Rivkin SE, Neilan B, Costanzi JH: A phase II trial of combination chemotherapy in patients with metastatic carcinoid tumors. A southwest Oncology Group Study. Cancer, 60 (12): 2891-2895, 1987.
11. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG: Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol, 23: 4897-4904, 2005.
12. Hage R, Seldenrijk K, de Bruin P, van Swieten H, van den Bosch J: Pulmonary large-cell neuroendocrine carcinoma (LCNEC). Eur J Cardiothorac Surg, 23: 457-460, 2002.
13. Battafarano RJ, Fernandez FG, Ritter J, Meyers BF, Guthrie TJ, Cooper JD, Patterson GA: Large cell neuroendocrine carcinoma: an aggressive form of non-small cell lung cancer. J Thorac Cardiovasc Surg, 130(1): 166-172, 2005.
14. Iyoda A, Hiroshima K, Moriya Y, Takiguchi Y, Sekine Y, Shibuya K, Iizasa T, Kimura H, Nakatani Y, Fujisawa T: Prospective study of adjuvant chemotherapy for pulmonary large cell neuroendocrine carcinoma. Ann Thorac Surg, 82 (5): 1802-1807, 2006.