Role of chemotherapy in gastro-entero-pancreatic neuroendocrine tumors : the end of a story ?

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Abstract

Gastroenteropancreatic Neuroendocrine Tumours (GEP NET) are heterogeneous and rare malignancies although their prevalence is increasing. Multiple therapeutic approaches are available to date for their management, including surgery, hormonal and immune radionucleide therapies and chemotherapy. The purpose of this review is to collect, examine, and analyze data available regarding contemporary chemotherapeutic management of GEP NET in order to determine whether or not chemotherapy still takes place in the therapeutic arsenal of GEP NET. We therefore performed a systematic search of all the English-spoken literature regarding GEP NET. Anthracyclins, 5-fluorouracil (5-FU), DTIC and streptozotocin are amongst the most commonly used chemotherapeutic agents, usually prescribed in combination. Their efficiency in reducing tumor burden is not always associated with better survival, perhaps due to severe toxicity. Chemotherapy in GEP NET is mainly devoted to poorly differentiated tumours, but also in well differentiated carcinomas either not eligible or resistant to other therapies. Chemotherapy remains therefore useful in specific cases of GEP NET management. However, a new era of antitumoral agents, such as targeted therapies, could eventually replace these old recipes in the near future. (Acta gastroenterol. belg., **2009**, 72, **49-53**).

Key words : chemotherapy, gastro-entero-pancreatic neuroendocrine tumors.

Introduction

Gastroenteropancreatic Neuroendocrine Tumours (GEP NET) are rare malignancies, with an overall incidence of 2 to 3 cases/100,000/year. They account for less than 2% of all digestive malignant tumors (1). Endocrine tumours (ETs) of the digestive tract include different subsets of malignancies, such as pancreatic endocrine tumours (PETs), gastrointestinal endocrine tumours anciently called carcinoid tumors, and other poorly differentiated gastroenteropancreatic NETs. Most of the tumours encountered in the digestive tract are well-differentiated and have an indolent course, although some, classified as poorly-differentiated neoplasms, could display a more aggressive behavior rendering these tumours more difficult to manage. Systemic chemotherapy had been for years the only effective treatment in the management of GEP NET, with a clear gain in terms of response rate and survival compared to either best supportive care or other treatments. However, new therapeutic approaches such as targeted therapies or peptide receptor radionuclide therapy have been developed during the last decade. They seem efficient, more specific, less toxic and therefore may dethrone systemic treatments in GEP NET management, rendering the usefulness of chemotherapy less clear.

The aim of the present article is thus to review the exact role of chemotherapy in the management of GEP NET at the beginning of the 21st century. A systematic search of all the English-spoken literature regarding GEP NET has therefore been performed, based on a MEDLINE search (Pubmed) carried out from January 1970 to September 2008. Approximately 45 trials, including over 500 patients have been retrieved from the literature, including randomized phase III studies, phase II trials and retrospective analyses.

We first would like to stress that major quality differences exist between studies, rendering results analysis rather thorny. The relative rarity of GEP NET implies that relatively few patients have been included in the above studies. Furthermore, heterogeneity in tumor stages, performance status, tumour progression status and previous therapeutic managements confuse data. Moreover, response evaluation based nowadays on WHO/RECIST criteria differ from those used in older studies (e.g. clinical and hepatomegaly response). These points may partly explain the differences in response rates between earlier and more recent studies and the difficulty to make an adequate comparison.

For the sake of clarity, and based upon the literature, GEP NET chemotherapy management has been divided

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Table 1. — **Combination therapies in poorly-differentiated endocrine tumours**

Authors	Regimen	N	ORR (%)	mOS (months)
Moertel (2)	CDDP + Et	18	67	19
Mitry (3)	CDDP + Et	41	41.5	15
Hou (4)	CDDP + CPT11	14	43	NR
Hainsworth (5)	P + Et + C	78	53%	14.5

C, carboplatin ; CPT11, irinotecan ; CDDP, cisplatin ; Et, etoposide ; P, paclitaxel ; ORR, overall response rate ; mOS, median overall survival ; NR, not reached.

in 3 groups : poorly-differentiated GEP NET, well-differentiated pancreatic endocrine tumours and gastrointestinal neoplasms.

Poorly-differentiated GEP NET (Table 1)

Poorly-differentiated GEP NET are very aggressive tumours, with a 6 months median overall survival (mOS) for untreated patients. They share several characteristics with endocrine lung tumours and are usually treated as such with cisplatin-based chemotherapy, regardless of the stage. These tumours are usually associated with a high rate of angioinvasion and high Ki-67 proliferative index witnessing the high risk of aggressive tumours. The Ki-67 protein is a proliferation antigen, which is present in G1, S, G2, and M phases of the cell cycle. Quiescent or resting cells in the G0 phase of the cell cycle do not express the Ki-67 antigen. The Ki-67 index seems to date the best available marker of proliferation. Based upon the literature, some authors have therefore suggested to consider Ki-67 as a prognostic factor determining the utility of a front-line chemotherapy in poorly-differentiated GEP NET management. Furthermore, other prognostic factors such as mitotic index, presence of angio- and/or perineural invasion, or p53 overexpression could also play a role in the therapeutic choice of GEP NET. To date, no randomized study is available ; therefore, our knowledge is based upon retrospective, feasibility and phase II trials.

Moertel and colleagues initially described a remarkable objective response rate (ORR) of 67% and a mOS of 19 months in 18 poorly-differentiated GEP NET treated with etoposide-cisplatin combination. Interestingly, well-differentiated GEP NET evaluated in parallel, responded poorly (ORR of 14%). Toxicities were a major concern for most patients, with grade 3/4 vomiting, pancytopenia, alopecia and peripheral neuropathy (2). Later, Mitry *et al*. reported similar results in a retrospective analysis of 41 poorly-differentiated GEP NET treated with the same regimen with a mOS of 15 months and a 41.5% ORR compared to 9% in the well-differentiated group. This combination was associated with significant toxicity, including high rate of grade 3-4 neutropenia (60%) and febrile neutropenia (14%) (3). Recently, a pilot study combining cisplatin and irinotecan showed a 43% ORR in poorly-differentiated GEP NET, associated with gastrointestinal and hematologic toxicities, classically encountered with both molecules (4). Hainsworth *et al*. described two years ago a phase II trial assessing a paclitaxel, carboplatin, and etoposide combination in 78 patients with histologically proven poorly differentiated endocrine carcinoma. Fifty-three percent showed major responses with a complete response rate (RR) of 15% and a mOS of 14.5 months. As observed in the previous described studies, toxicity was a major issue, with grade 3/4 neutropenia in 82% of patients. Three patients died as a consequence of neutropenic sepsis rendering this combination too toxic (5). Based upon these studies, cisplatin and etoposide combination seems to have the better balance between efficacy and toxicity and is therefore considered as standard in this tumour population.

Well-differentiated pancreatic endocrine tumours (WDPETs)

Patients with WDPETs are characterised by a prolonged survival (40 months mOS versus 6 months for poorly-differentiated endocrine carcinomas). They are considered rather chemosensitive (6,7). Streptozotocin (STZ) has been the main agent used in this tumour type, especially because it is well established that STZ selectively targets pancreatic islet cells, possibly through a transport system that is present on pancreatic b-cells (8). However, other drugs, such as anthracyclins or dacarbazine (DTIC) have also been used, with variable success.

Single Agent therapies

Twenty years ago, Broder and colleagues reported radiological and biochemical response rates of 50 and 64% in 52 WDPETs patients treated with STZ (9). Later, Moertel *et al*. showed, in 42 patients, a 36% ORR along with a 16 months median survival (7). Both studies demonstrated a particularly high rate of nausea and vomiting (83 and 94%, respectively), whereas 29 and 65% of the patients experienced renal toxicity, sometimes severe (19% of grade 3-4) (9).

A phase II trial using doxorubicin monotherapy included 20 patients suffering from progressive and pretreated WDPETs. Authors showed a 20% ORR with a 6 months mOS. Treatment was associated with high rates of nausea, vomiting and alopecia. Congestive heart failure, a typical anthracyclin dose-related toxicity, was also observed in one patient (10).

DTIC, a synthetic alkylating agent active in malignant

melanoma, has been studied in a phase II trial demonstrating a 33% ORR in 42 patients suffering from advanced PNET, with a 19 months mOS (11). Grade 3-4 neutropenia, observed in 18% of the cases, was the commonest toxicity, whereas severe vomiting was experienced by 13% of the population.

Finally, other drugs such as paclitaxel and gemcitabine have also been tested as single therapies, without convincing efficacy (12,13).

Combination chemotherapy (Table 2)

The next logical step consisted in combining these active molecules. A randomized trial performed by Moertel and colleagues, comparing STZ + 5-Fluorouracil (5-FU) versus STZ alone, demonstrated a 63% ORR and a 26 months mOS for the combination versus 36% and 16.5 months for STZ alone (6). Later, the same author, demonstrated in a prospective randomized trial comparing doxorubicin + STZ, STZ + 5-FU and chlortozotocin, an ORR of 69% and a 26.5 months mOS in the doxorubicin + STZ arm. These results were significantly better than observed in the other 2 regimens (Table 2). This combination became therefore the standard therapy for progressive WDPETs (7).

However, due to the relative rarity of WDPETs, both of the above studies included relatively few patients. Furthermore, many were quite heterogeneous with various tumor stages, performance status, and previous therapeutic managements. Evaluation criteria were previously rather subjective (e.g. clinical and hepatomegaly response) and differ a lot from actual WHO/RECIST methods of evaluation. This last point may partly explain the differences in response rates between earlier and more recent studies as shown in Table 2 (14,15).

Temozolomide, an oral prodrug of DTIC with better bioavailability profile, has been studied in combination with diverse other drugs such as thalidomide, bevacizumab and capecitabine. These combinations might deserve further investigations taking into account the results published in the literature. In a phase II trial studying temozolomide in combination with thalidomide in advanced GEP NETs, 11 patients suffering from PETs were treated. One complete response (CR) and 4 partial responses (PR) were observed in this group. This regimen seems to be especially active in pancreatic tumors (16). Another phase II studied temozolomide combined with bevacizumab in eighteen highly pretreated PETs patients. Four of them (24%) experienced PR whereas 12 (70%) had stable disease (SD) (17). Experience with temozolomide and capecitabine has been reviewed retrospectively in 17 patients with PETs. One patient achieved a CR, and nine a PR with a median duration of partial response of 284 days (18). Altogether, these combinations seem effective in PETs and therefore deserve further future investigations.

In order to improve results obtained with doublets, triple cytotoxic combinations with either 5-FU + doxorubicin + STZ or 5-FU + DTIC + epirubicin have been studied without any clear evidence of better results compared to doublets therapies. Kouvaraki *et al*. retrospectively reviewed 84 patients treated at MD Anderson Cancer Center with triplet combinations. The ORR was 39%, and 50% achieved a stable disease (SD). In terms of response, no differences were observed between locally advanced and metastatic tumors. Median progression-free survival (PFS) and PFS at 2 years were 18 months and 41% respectively ; mOS and overall survival (OS) at 2 years were 37 months and 74%, respectively (19). Due to the disagreement regarding the therapeutic effect of the classical chemotherapy regimens used in PETs, several groups have studied other combinations. The Italian Trials Medical Oncology group evaluated the efficacy of a combination of 5-FU, DTIC, and epirubicin and its dose intensification. Their pooled data published in 2002 included 28 patients with pancreatic tumors. Among these, one complete response (CR), seven partial responses (PR), and eight stabilizations were observed (20).

Other combination drug regimens tested to date do not demonstrate any clear advantage over this two-drug regimen, whether in terms of response or survival (21-22).

Table 2. — **Pancreatic neuroendocrine tumor : doublets and triplets combinations in pancreatic endocrine tumors**

Authors	Regimen	N	ORR (%)	mOS (months)
Moertel (6)	S / S + 5-FU	42 / 42	36 / 63	16.5 / 26
Moertel (7)	D + S / C / S + 5-FU	38 / 33 / 34	69 / 30 / 45	26.5 / 18 / 16.8
Delaunoit (14)	D + S	45	36	22.4
Cheng (15)	D + S	16	6	NR
Kouvaraki (19)	5-FU + D + S	83	39	37
Bajetta (20)	DTIC + E + 5-FU	28	28	/
Rougier (21)	D + CDDP + 5-FU	24	15	27
Rivera (22)	D + S + 5-FU	12	54	21

C, chlortozotocin ; CDDP, cisplatin ; D, doxorubicin ; DTIC, dacarbazine ; E, epirubicin ; Et, etoposide ; S, streptozotocin ; 5-FU, fluorouracil ; ORR, overall response rate ; mOS, median overall survival ; NR, not reached after a median follow-up of 10 months.

Table 3. — **Chemotherapy in carcinoid tumors**

Authors	Regimen	N	ORR (%)	mOS (months)
Moertel (27)	STZ + 5-FU / 5-FU + Cy	59/59	33 / 26	/
Bukowski (30)	5-FU + D / 5-FU + S	82 / 81	16 / 16	15.7 / 24.3
Oberg (29)	5-FU + S	31	9	22

D, doxorubicin ; S, streptozotocin ; 5-FU, fluorouracil ; Cy, Cyclophosphamide ; ORR, overall response rate ; mOS, median overall survival.

Chemotherapy in gastrointestinal NETs

Gastrointestinal NETs are the most frequent NETs, with the latest data estimating it at around four cases per 100.000 population per year (1). As for PETs, several agents, used alone or in combination, have been assessed, with more or less benefits for the patients.

Single agents

Several drugs have been evaluated in that setting, including, STZ, DTIC, gemcitabine and taxanes. None of these drugs demonstrated any positive results in terms of response or survival (12,13,23-26).

Combination therapies

The most frequently assessed combination is STZ and 5-FU. Moertel *et al*. randomized 118 patients suffering from gastrointestinal NETs, either to receive STZ plus 5-FU or STZ plus cyclophosphamide. They reported an ORR of 33 and 26%, respectively, without any significant difference in patient survival between the two treatment arms (27). Single-agent doxorubicin compared to STZ plus 5-FU has been studied by Engstrom *et al*. in 172 patients suffering from progressive CTs. No difference was seen between both groups in terms of ORR (22% for the combination treatment and 21% for doxorubicin). Toxicities were similar in both arms, although renal insufficiency was mostly observed in the STZ arm (28). Oberg *et al*. observed a 9.7% ORR and 58% of SD in 31 patients treated with the same combination, with a mean remission time of 2.7 months and a mOS of 22 months (29). A randomized phase III trial comparing 5-FU+ doxorubicin and STZ + 5-FU included 163 patients with gastrointestinal NETs. Results in terms of ORR (15.9 vs 16%, $P = 0.82$) or progression free survival (PFS) (4.5 vs 5.3 months, $P = 0.17$) did not show any differences between both groups. However, STZ / 5-FU was superior to 5-FU / doxorubicin in mOS (24.3 vs 15.7 months, $P < 0.02$) (30). Finally, in the Cleveland Clinic Foundation, 65 patients were randomized to 5-FU plus cyclophosphamide plus STZ with (n = 56) or without doxorubicin (n = 9). They observed a RR of 31 and 22% respectively, with a mOS of 10.8 months, identical in both groups (31).

Many other combination chemotherapies have been tested, including 5-FU + DTIC + epirubicin (18,32), 5-FU + DTIC + leucovorin (33) and temozolomide + thalidomide (14).

Considering all these results, chemotherapy should not be considered as an upfront treatment for patients with advanced gastrointestinal NETs. Using anti-tumoral agents such as STZ and 5-FU should be devoted to tumours not responding to other therapies.

Conclusions

Chemotherapy has been used for years in the management of metastatic or locally advanced GEP NETs, with more or less success. Some drugs, such as anthracyclins, cisplatin, STZ, 5-FU and DTIC are clearly effective, alone or in combination, especially in the management of pancreatic NETs. However, guidelines are lacking when considering the role of these drugs in the therapeutic arsenal of these rare neoplasms. Aggressive poorly-differentiated carcinomas must be treated by cisplatin-based chemotherapy. These tumours are usually associated with a high rate of angioinvasion and high Ki-67 proliferative index witnessing the high risk of developing aggressive systemic disease. It is therefore suggested by some authors to consider Ki-67 as a prognostic factor determining the utility of a front-line chemotherapy in GEP NET management.

The role of front-line chemotherapy for well-differentiated GEP NET is less clear. Generally, these tumours are slow-growing and do not necessitate aggressive and potentially toxic therapies. Efficient biologic treatments (eg. octreotide) are now available in that setting, with easily manageable side effects and predictable activity. The role of chemotherapy is therefore mainly indicated to tumours for whose other treatments are either contra-indicated or ineffective in patients with proven progressive disease. Authors must emphasize that STZ is not reimbursed in Belgium, rendering standard treatment administration quite difficult. We therefore need, more than other countries, new therapeutic agents to replace STZ in the therapeutic arsenal of these rare tumours.

Research agenda

New therapeutic agents, such as oxaliplatin or irinotecan, as well as new targeted therapies, used alone or in combination must be studied in the future in order to determine their benefit in these particular neoplasms. Furthermore, as for other tumours, a better candidate selection, based upon predictive validated clinical, pathological, and molecular factors, should become a

masterpiece in the clinician therapeutic decisions.

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