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Chapter 5

Combinational chemotherapy and radiotherapy

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The treatments of neuroendocrine tumors (NETs) is mainly based on their biological characteristics of aggressiveness and functional features. Radical surgery is the sole effective approach, whereas in other cases hormonal treatment is the choice for well-differentiated tumors and chemotherapy for aggressive diseases. Several chemotherapy agents have been employed either as single agent or in combination in the treatment of advanced stage NETs. Nowadays there are no indications for the use of chemotherapy in adjuvant or neoadjuvant treatment. The radiotherapy option in NETs is based on radiopharmaceuticals targeting receptors over-expressed by these diseases and radiopharmaceuticals acting on the cell metabolism.

The WHO classification issued in 2010 divides gastroenteropancreatic neuroendocrine tumors (NETs) into the following categories: NETs G1 (characterized by a low grade of malignancy), NETs G2 (more aggressive), neuroendocrine carcinoma G3 (with a high grade of malignancy and a poor prognosis), mixed adenoneuroendocrine carcinoma, hyperplastic and paraneoplastic lesions [1]. The classification of lung tumors is still based on the paper by Travis [2] who recognized the following four categories: typical carcinoid, atypical carcinoid, small-cell lung cancer and large cell neuroendocrine carcinoma. Typical carcinoids are generally less aggressive than atypical carcinoids, which are less aggressive than small-cell carcinoma (poorly differentiated NETs). The treatment of NETs is mainly based on their biological characteristics of aggressiveness and functional features, such as symptoms and endocrine markers. When feasible, radical surgery remains the sole effective approach, whereas in other cases hormonal treatment is the treatment of choice for NETs G1 and G2 and lung carcinoid, as well as chemotherapy for progressing disease and aggressive NETs. The clinical results obtained with chemotherapy strongly vary on the basis of the utilized agents and on the prognostic characteristics of NETs. In particular, the variable most likely predictive of responsiveness lies in the very high proliferating index (>10–15%). The partial response rates range from 40 to 60% with a median duration of 6 months with the combination of cisplatin and etoposide in undifferentiated NETs. Consequently, chemotherapy with platinum compounds is considered the standard treatment for patients with aggressive NETs. Conversely, fluoropirimidine combination should be the standard treatment for patients with well-differentiated NETs progressing during somatostatin analog treatments [3].

Chemotherapy in gastroenteropancreatic NETs

Several chemotherapy agents have been employed either as single agent or in combination in the treatment of advanced-stage NETs, as streptozotocin (STZ), doxorubicin (DOX), 5-fluorouracil (5-FU), cisplatin, etoposide (VP16) and dacarbazine (DTIC). Recently, some new chemotherapeutic agents have become available, such as temozolomide (TMZ), oxaliplatin, capecitabine, irinotecan and gemcitabine. Taking into account the lack of clinical studies in these setting, nowadays there are no indications of chemotherapy in adjuvant or neoadjuvant treatment. The obtained clinical results strongly vary on the basis of the utilized agents and on the prognostic characteristics of NETs. In particular, the variable most likely predictive of responsiveness lies in the very high proliferating index (>15%).

Poorly differentiated histology and tumor primary sites in pancreas are characterized by good responsiveness to chemotherapy treatment. On the contrary, ileal and appendicular neuroendocrine tumors, usually highly differentiated and with a low proliferating index, do not benefit from chemotherapy

Well-differentiated gastroenteropancreatic NETs

Single-agent chemotherapy with STZ yielded a tumor response rate of 36–42%, but these early studies can be criticized with respect to the rough methods of interpreting morphological responses. Other monotherapies, including chlorotozotocin, DOX, 5-FU and DTIC, have been used, but criticized owing either to the high toxicity rate or lack of objective response. Monotherapy strategies have been universally replaced by combination chemotherapy protocols. As seen in Table 5.1 [4], many combinations have been used, with STZ, 5-FU and anthracyclines forming the cornerstone of the tested regimens. In well-differentiated pancreatic endocrine tumors, the results obtained by Moertel *et al.* using STZ and DOX so far have not yet been improved, with a 69% objective response rate and a median survival of 26 months; these results should be compared with an objective response rate of 45% for 5-FU and STZ. The same group had previously obtained better results with 5-FU in combination with STZ in a Phase III trial, in comparison with STZ monotherapy. While no group has managed to achieve the same response rates, objective responses of 36–55% have been established using STZ and DOX, with the exception of one study where a response rate of 6% was reported in a group of 16 patients. The author questioned the reliability of Moertel's earlier studies, especially their methods of measuring responses. However, three recent studies have reported good response rate using well-defined criteria for recruitment and evaluation. Strosberg *et al.* reported that the combination of capecitabine and TMZ is associated with a high and durable response rate in metastatic endocrine carcinomas of the pancreas, superior to those observed with STZ-based regimens [5]. As for well-differentiated gastroenteropancreatic (GEP) tumors of the pancreas, single-agent regimens have been largely disappointing in GEP tumors of midgut origin, with objective response rates of <25% and response durations rarely exceeding 3 months. In 1979, Moertel *et al.* combined 5-FU with STZ in midgut carcinoids, yielding a response rate of 33%. Later studies using the same combination have failed to reproduce these results (Table 5.1). Therefore, other drug combinations have also been examined but, apart from a 40% objective response rate for patients with midgut carcinoids treated with DOX and STZ in a Phase II study, no other reliable cytotoxic regimen has been found for patients with advanced or metastatic disease of midgut origin [6].

Poorly differentiated gastroenteropancreatic NETs

Standard treatment of patients with advanced poorly differentiated GEP tumors has largely been based on protocols containing VP16 and cisplatin (Table 5.2) [7]; such patients are rarely sensitive to combination therapy

Table 5.1. Chemotherapy in well-differentiated gasteroenteropancreatic neuroendocrine tumors.

Study (year)	Type of tumor	Regimen	Patients (n)	Objective response (%)	Response duration (months)	Median survival (months)	Ref.
Moertel and Hanley (1979)	Carcinoids	5FU + cyclophosphamide STZ + 5-FU	47 42	33 33			[20]
Moertel (1980)	Pancreatic	STZ STZ + 5-FU	42 42	36 63	17 17	17 26	[21]
Engrstom (1984)	Carcinoids	STZ + 5-FU DOX	80 81	22 21	8 6.5	16 12	[22]
Frame (1988)	Carcinoids	DOX + STZ	33	40		11	[23]
Eriksson (1990)	Pancreatic	DOX + STZ	25	36	22		[24]
Moertel (1992)	Pancreatic	DOX + STZ + 5-FU STZ	36 33	69 45	18 14	26 18	[25]
Bukowski (1992)	Carcinoids	DOX + STZ+ 5-FU + cyclophosphamide STZ + 5FU + cyclophosphamide	56 9	31 22		 10.2	[26]
Di Bartolomeo (1995)	Carcinoids	DOX + DTIC + 5-FU	20	10		5	[27]
Bajetta (1998)	Carcinoids	Epirubicin + 5-FU + DTIC	15	27	10		[28]
Cheng and Saltz (1999)	Pancreatic	DOX + STZ	16	6	18		[29]
McCollum (2004)	Pancreatic	DOX + STZ	16	6	3.9	20.2	[30]
Kouvaraki (2004)	Pancreatic	DOX + STZ + 5-FU	84	39	9.3	40	[31]

5-FU: 5-fluorouracil; CAP: Capecitabine; DTIC: Dacarbazine; DOX: Doxorubicin; STZ: Streptozotocin; TEM: Temozolomide.
Adapted from [4].

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Table 5.1. Chemotherapy in well-differentiated gasteroenteropancreatic neuroendocrine tumors (cont.).

Study (year)	Type of tumor	Regimen	Patients (n)	Objective response (%)	Response duration (months)	Median survival (months)	Ref.
Sun (2005)	Carcinoids	DOX + 5-FU STZ + 5-FU	25 27	15.9 16	4.5 5.3	15.7 24.3	[32]
Delaunoit (2008)	Pancreatic	STZ + DOX	45	36			[33]
Strosberg (2011)	Pancreatic	TEM-CAP	30	70	18		[5]

5-FU: 5-fluorouracil; CAP: Capecitabine; DTIC: Dacarbazine; DOX: Doxorubicin; STZ: Streptozotocin; TEM: Temozolomide.
Adapted from [4].

with STZ, DTIC and 5-FU. Others studies were conducted with cyclophosphamide, DTIC and vincristine, recording an unsatisfactory response duration. A study involving the combination of 5-FU, epirubicin and DTIC showed a lower response rate compared with the regime with cisplatin and etoposide. While tumor response rates are often good (42–65%), duration of response rarely excedes 10 months and median survival is of the order of 15 months. The guidelines state that a cisplatin + VP16 regimen is indicated; however XELOX (capecitabine and oxaliplatin) or FOLFOX (5-FU, lederfolin and oxaliplatin) chemotherapy regimens [8] or even the combination of cisplatin with a molecular targeted therapy can be considered as backup. New options are required for the treatment of these patients.

Chemotherapy in thoracic NETs

Neuroendocrine tumors of the thorax include both bronchial and thymic NETs. No adjuvant chemotherapy or chemoradiation is recommended for well-differentiated tumors. G1/G2 bronchial NETs are generally less responsive to chemotherapy than small-cell lung cancer. However, platinum-based regimens may be considered and have reported activity in patients with more aggressive/intermediate grade

Table 5.2. Chemotherapy in poorly differentiated gastroenteropancreatic neuroendocrine tumors.

Study (year)	Regimen	Patients (n)	Objective response (%)	Response duration (months)	Median survival (months)	Ref.
Moertel (1991)	VP16 + CDDP	18	67	8	19	[34]
Seitz (1995)	Vp16 + CDDP	11	54			[35]
Mitry (1999)	VP16 + CDDP	41	42	9	15	[36]
Bajetta (1998)	5-FU + epirubicin + DTIC	15	27	10		[28]
Fjallsskog (2001)	VP16 + CDDP	36	47	9		[7]
Bajetta (2007)	XELOX	38	63	8.5	23.5	[8]

5-FU: 5-fluorouracil; CDDP: Cisplatin; DTIC: Dacarbazine; VP16: Etoposide; XELOX: Capecitabine and oxaliplatin.
Adapted from [4].

tumors. The use of various chemotherapeutic agents (DOX, 5-FU, DTIC, cisplatin, etoposide, STZ and carboplatin) in the treatment of bronchopulmonary (BP) carcinoids has yielded minimal (20–30%), mostly short-lasting results, and an effective chemotherapeutic regimen for unresectable disease is still lacking. Combination chemotherapies for BP carcinoids are usually platinum and STZ-based. Owing to the low response rates for chemotherapy in BP carcinoids combined with serious side effects, the indication to use currently available chemotherapeutic regimens is limited [9]. Results from a published Phase II trial suggest antitumor activity with single-agent temozolomide for well-differentiated NETs [10]. In small studies, large-cell neuroendocrine carcinoma has been shown to have a low and partial response rate to preoperative or postoperative chemotherapy but it prolongs survival in lower-stage disease [11–12]. The standard of care for limited-stage small-cell lung cancer includes early thoracic radiotherapy combined with cisplatin and etoposide. Extensive-stage disease is primarly treated with chemotherapy with VP16 and platinum compound, considered as the reference treatment for inoperable poorly differentiated NETs [7].

Other NETS

Medullar carcinoma of the thyroid gland

Medullar carcinoma of the thyroid gland shows low response rate to chemotherapy. In advanced disease, the single agent with reported activity

was DOX. Other active regimens are cyclophosphamide, epirubicin, vinblastine combination and 5-FU, STZ and epirubicin.

Merkel cell carcinoma

The role of adjuvant therapy is debated. In advanced disease, high response rates are obtained with cisplatin and VP16 regimen or cyclophosphamide, epirubicin and vinblastine combination. None of these regimens have an impact on survival.

Pheochromocytoma

In advanced disease, the active treatment, especially for symptomatic control, is cisplatin, DTIC and vindesine regimen, with high impact on response rate and not on survival.

Radiotherapy in NETs

The treatment of NETs with radiopharmaceuticals is possible today, both for radiopharmaceuticals targeting receptors overexpressed in these diseases and also with radiopharmaceuticals acting on the cell metabolism. Different receptors have been investigated as a target of the radioisotope; however, until now the somatostatin receptors (SSTRs) seem to be the best option. The radiopharmaceuticals targeting SSTRs are based on three components: a peptide, a chelator and a radionuclide. The first somatostatin analog synthesized was octreotide; the substitution of phenylalanine at position 3 with a tyrosine residue produced Tyr3-octreotide (TOC). This increased the affinity for SSTR2 receptors. Replacing the C-terminal threoninol with threonine resulted in the synthesis of Tyr3-octreotate (TATE), which has been shown to have much higher affinity for SSTR2 compared with octreotide. Many other analogs have been developed by substituting chemical groups with the aim of enhancing the affinity of the analogs for the receptors. Among them, one of the most recent is Nal3-octreotide, Nal3-octreotate (Nal3-octreotide-ATE) obtained by substituting a naphtyl-alanine in position 3. An important part of these radiopharmaceuticals is the radioisotope that is bound to pepdide through the chelator diethylentriaminepenta-acetic-acid or tetra-azacyclododecanetetra-acetic-acid (DOTA).

The most relevant radiopharmaceuticals that should be cited for peptide Ac radioreceptor therapy (PRRT) are (Table 5.3):

- ^{111}In-pentetreotide (Octreoscan®)
- ^{90}Y-DOTA (Tyr3) TOC
- ^{177}Lu-DOTA (Tyr3) TATE

Ac Radioreceptor therapy Treatment with radiopharmaceuticals targeting receptors overexpressed by these diseases and also with radiopharmaceuticals acting on the cell metabolism

Table 5.3. Radiotherapy in neuroendocrine tumors.

Study (year)	Radiopharmaceutical	Patients (n)	Clinical benefit (%)	Ref.
Valkema (2002)	^{111}DTPA-octreotide	26	66	[13]
Otte (2002)	^{90}Y-DOTATOC	29	96	[14]
Bodei (2003)	^{90}Y-DOTATOC	141	76	[15]
Kwekkebom (2003)	^{177}Lu-DOTA-TATE	310	46	[17]

Valkema *et al.* treated 26 patients with GEP-NETs with high doses of ^{111}In-diethylentriaminepenta octreotide, receiving a total cumulative dose of more than 20 GBq. The results were 8% partial response (PR) and 58% stable disease (SD). In other studies, patients were treated with high cumulative activities (up to 36.6 GBq) and 17% of them had PR with 58% SD. In all studies, the most common toxicity was bone marrow suppression [13].

Therapy with ^{90}Y-DOTATOC was performed by Otte *et al.* who treated 29 patients with GEP-NETs using a dose-escalating scheme of four or more cycles of ^{90}Y-DOTATOC, up to a cumulative dose of 6.120 ± 1.347 MBq/m^2. The results were: 24 patients had SD, two had PR and three had PD [14]. Bodei *et al.* published data of a Phase I study in 21 patients with GEP-NETs. Cumulative total doses given in two cycles ranged from 5.9 to 11.1 GBq. The results were 29% PR with a median duration of response of 9 months. The same group evaluated the objective response of 141 patients with various types of NETs treated with doses higher than 7.4 GBq of ^{90}Y-DOTATOC (cumulative activity 7.4–26.4 GBq) divided into two to 16 cycles. An overall clinical benefit (complete response [CR]+ PR + SD) was observed in 76% of patients [15]. However, in most trials, a better overall response is achieved when using ^{90}Y-DOTATOC for GEP-NETs with a 10–30% improved therapeutic effectiveness.

The advantage of using ^{177}Lu-DOTA-TATE is the better tumor/kidney, spleen and liver uptake ratio, which allows higher tumor absorbed doses without major effects on the dose-limiting organs, and also the longer residency time of ^{177}Lu-DOTA-TATE in tumors and the γ-emission of ^{177}Lu [16]. Most of the studies using ^{177}Lu-DOTA-TATE have been performed by Kwekkeboom *et al.* who propose ^{177}Lu-octreotate as the radiolabeled somatostatin of choice when performing PRRT. In 2003, the author assessed the effects of ^{177}Lu-DOTA-TATE in 34 patients with GEP tumors. The results were 3% CR, 35% PR, 41% SD and 21% PD. Following this study, they treated 131 patients with GEP tumors with a cumulative dose of 22.2–29.6 GBq of ^{177}Lu-DOTA-TATE: three obtained a CR (2%), 32 a PR (26%), 24 a minor response (MR; 19%), 44 had SD (35%) and 22 developed PD (18%). In a more extensive study by the same group, the efficacy of ^{177}Lu-DOTA-TATE was evaluated in 310 patients and toxicity was evaluated in 510 patients each receiving a cumulative radiation dose of 27.8–29.6 GBq in four treatment cycles with 6–10-week intervals between each cycle. CR was seen in 2%, PR in 28% and a MR in 16% of patients. Acute side effects such as nausea and vomiting occurred after 25 and 10% of administrations, respectively. Subacute WHO hematological toxicity (grade 3 or 4) occurred in 3.6% of treatment cycles. Delayed toxicities included serious liver toxicity in two patients and myelodysplastic syndrome in three patients [17]. Experience by Kwekkeboom *et al.* have lead them to conclude that the two significant factors predicting favorable treatment outcome when using ^{177}Lu-ocreotate were a high patient performance score and high uptake on the pretreatment Octreoscan [18].

The current studies are carried out mainly on progressive disease, which is resistant to traditional treatment or relapsed. However, other clinical indications should be investigated when the tumor mass is still small or in minimal residual disease. Therapy might be improved by combining different radionuclides, ^{177}Lu and ^{90}Y, or establishing new treatment schemes in combination with chemotherapy, immunotherapy or external-beam irradiation

In order to increase the efficacy of the PRRT, an alternative option is to combine ^{90}Y-DOTA-TATE with ^{177}Lu-DOTA-TATE. In this way, the irradiation of tumor mass is performed by a radioisotope with low energy and short range (^{177}Lu) followed by a radioisotope with higher energy and wide range (^{90}Y). The preliminary results, in an ongoing trials, on 26 patients with advanced GEP-NETs yielded 4% of CR, 38% of PR and 50% SD. In conclusion, radiolabeled somatostatin analogs show a good efficacy as therapeutic agents for PRRT in NETs (tumor reduction, improvement of quality of life, and biochemical response). Only a small number of serious adverse effects occurred and only in those patients who had previous chemotherapy [19].

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Summary

- The unquestionable role of chemotherapy in the treatment of neuroendocrine tumors must be correlated with the expression of the biological and clinical variables predictive of the evolution of the disease and of responsiveness to the different available treatments.
- At the same time, the development of radiotherapy option with a good efficacy and small number of serious adverse events requires to improve the different combination treatments.

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