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Review of recent advances in medical treatment for neuroendocrine neoplasms: somatostatin analogs and chemotherapy

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ABSTRACT

Neuroendocrine neoplasms (NENs) are a heterogeneous group of rare tumours often producing high levels of hormones and causing symptoms. There are a number of different types of NENs. They usually arise as advanced and low/intermediate grade only in a minority of cases, as high grade. Treatment depends on which type and may include surgery, interventional radiology, and systemic treatment, including chemotherapy, somatostatin analogs, interferon α2b, peptide receptor radionuclide therapy, and only for pancreatic neuroendocrine tumors, molecular targeted agents, including everolimus and sunitinib. The aim of the article is to review the medical approaches with somatostatin analogs and chemotherapy. The treatment of NENs is mainly based on their biological characteristics of aggressiveness and functional features, such as symptoms and endocrine markers.

Key words: Neuroendocrine neoplasms; somatostatin analogs; chemotherapy; peptide receptor radionuclide therapy; molecular targeted agents

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a group of tumours arising from various different epithelial cells with patterns of neuroendocrine differentiation, usually from the gastrointestinal tract and the bronchopulmonary system.[1] The World Health Organization (WHO) 2010 classification distinguishes this class of diseases between well differentiated and poorly differentiated neuroendocrine carcinomas.[2] The choise of appropriate treatment depends on their biological and morphological characteristics, functional status, and disease stage. Surgery is the best option for resectable tumours, whereas in cases of locoregional unresectable and metastatic disease, therapeutic options include somatostatin analogs (SSAs),[3] inhibitors of the mammalian target of rapamycin,[4-6] receptor tyrosine kinase inhibitors,[7,8] chemotherapy,[9] and pepetide receptor radionuclide therapy (PRRT).[10]

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In recent years, strong evidence has emerged of an antiproliferative effect of SSAs on NENs, thought to occur via direct and indirect mechanisms.[11] The direct mode of action involves interaction with somatostatin receptors on tumor cells leading to activation of phosphotyrosine phosphatases[12] and modulation of the mitogen-activated protein kinase signaling pathway.[13] The indirect antiproliferative effect occurs through inhibition of expression of growth factors, such as insulin-like growth factor and vascular endothelial growth factor.[14] Activities of SSAs are mediated by interaction of somatostatin with a series of five receptors (SSTRs) encoded by five different genes belonging to the class of receptors linked to transmembrane G-proteins, able to inhibit cAMP. Therapeutic activity is achieved through interaction with two of the five SSTRs and, more precisely, with subtypes 2 and 5, for which there is the highest affinity.[15]

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Octreotide and Lanreotide are the two SSAs adminsitered by injection. Octreotide was the first SSA for the treatment of hormone-producing pituitary, pancreatic and intestinal neuroendocrine tumors (NETs).[16] Lanreotide has a similar mechanism of action, also displays high-affinity binding for types 2 and 5, has low affinity for types 1 and 4 and medium affinity for type 3.[17]

Several chemotherapy agents have been employed, either as single-agent or in combination for advanced-stage disease in poorly differenctiated NENs,[18,19] but also in well- and moderately differentiated tumors in advanced disease.[20-22] These agents are streptozotocin, doxorubicin, 5-fluorouracil, cisplatin, etoposide, and dacarbazine. Recently, some new chemotherapeutic agents have come available, such as temozolomide, oxaliplatin, capecitabine, irinotecan, and gemcitabine. Also a new way of chemotherapy administration is metronomic chemotherapy.[23,24] This overview details the evolution of SSAs and various chemotherapy combinations and their application to the management of NENs.

SOMATOSTATIN ANALOGS

In 1972, at the Salk Institute in La Jolla, California, a growth hormone (GH)-releasing antagonist (SST) was incidentally identified in the sheep hypothalamus during the search for a GH releasing hormone.[25,26] Crude extracts of sheep hypothalamus added to *in vitro* anterior pituitary cells caused an inhibition of GH secretion. After purification, a single compound accounting for all the GH-release inhibiting acitivity of the crude extract was isolated, and its primary structure, a 14-amino acid peptide, was identified.[26] The SST neuropeptide family (also known as somatostatin release-inhibiting factors) comprises peptides that originate from different post-translational processing of a 116 amino acid precursor (pre-proSST), which is encoded by a single gene located in humans on chromosome 3q28. Pre-proSSA is processed to pro-SST (96 amino acids), which is further cleaved to produce two bioactive proteins, the predominant, but functionally less active SST molecule consisting of 14 amino acids (SST-14), and a larger more potent molecular form, SST-28.[27] Twenty years after the discovery of SST in 1972, molecular cloning lead to the identification of its receptor structure.[28] Subsequently, it became apparent that in mammals, SST mediates its inhibitory effects through binding to at least five high-affinity G-protein-coupled membrane receptors.[29] Somatostatin (SST) and its analogs (SSAs) inhibit multiple cellular functions, including secretion, motility and proliferation and its action is mediated by somatostatin receptors sst1-5. These five receptors bind the natural peptide with high affinity, but only sst2, sst3 and sst5 bind the short synthetic analogues used to the treat neuroendocrine tumours (NET). SSAs have been used successfully to treat functional gastro-entero-pancreatic (GEP) NETs for more than a quarter of a century.[3] The main reason of the use of SSAs is the expression of somatostatin receptor subtypes in 80-90% of GEP-NETs according to autoradiographic or scintigraphic studies.[30,31] The biological effects of SSAs occur in relation to receptor subtype interaction. Inhibition of secretion appears to be largely mediated via the effects of the sst2 subtype, and all commercially available SSAs have appreciable affinity for sst2. However, proliferation in endocrine tissue may be mediated via other receptor subtypes. In patients with well-differentiated, slow-growing tumours, SSAs may be considered the first-line treatment with relatively good objective response rates and an excellent safety profile. The most used formulations of SSAs are long-acting-release (LAR) Octreotide (10-20-30 mg) and Lanreotide autogel (60-90-120 mg). These drugs are very effective at controlling tumor-related symptoms in the so called "functioning tumors" (symptomatic responses occur in 60-100% of patients).[32] Furthermore, they are able to significantly decrease specific tumor markers (i.e. urinary 5-hydroxy indole acetic acid and circulating Chromogranin A) in greater than 50% of patients. They are well-tolerated and safe, with a high tolerability rate even through a long period of treatment. Side effects, which occur in 20-50% of cases, are usually mild and do not require drug discontinuation. The most frequent side effects are the development of gallstones, pain at the site of application, abdominal pain, flatulance, nausea, asthenia, and glucose intolerance.[32] First-line systemic therapy for NETs often consists of SSAs such as octreotide acetate (Sandostatin®; Novartis Pharmaceutical Company, East Hanover, NJ, United States) or lanreotide (Somatuline®; Ipsen Pharmaceuticals, Paris, France). These drugs, initially developed to palliate the symptoms of Carcinoid Syndrome, have an inhibitory effect on secretion of gastrointestinal hormones (i.e. serotonin). Accumulating data indicate that SSAs are also capable of inhibiting NET growth[33,34] and have been demonstrated in numerous studies to represent the best available agents to induce symptomatic relief in patients with somatostatin receptors (sstr)-positive, hormone-producing NETs. The symptoms they control differ depending on tumour location and which amines/peptides are produced, but include sweating, flushing, diarrhea, and bronchospasm. There has been a controversy regarding the relative efficacy of octreotide and lanreotide. Most studies include both primary and secondary treatment with no stratification of the cohort before analysis. Although it is generally considered that the available SST analogs have a similar efficacy in treating hormone induced NET symptoms, some differences in response may exist.[3]

OCTREOTIDE

Octreotide (SMS201-995) was the first available SSAs and was introduced into clinical practice in 1983 for treatment of hormone-producing pituitary, pancreatic, and intestinal NETs.[16] As octreotide is incompletely absorbed after oral administration, its efficacy relied upon intravenous or subcutaneous injection. The standard dose of octreotide

varies from 0.1 mg to 0.3 mg subcutaneously two to three times daily, but doses up to 3 mg/day may be necessary for symptom control. The LAR formulation of octreotide is commonly used for the chronic management of symptoms in patients with carcinoid syndrome. Standard doses are 20 mg to 30 mg, intramusculary, every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels are not achieved for 10 to 14 days after LAR injection. Short-acting octreotide (usually 150-250 mcg subcutaneously 3 times daily) can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.[35,36] A randomized study comparing daily injection with octreotide to octreotide LAR every 4 weeks in the symptomatic treatment of 93 patients noted at least as good symptomatic efficacy for depot octreotide at various dosages (10, 20, 30 mg) compared to subcutaneously octreotide.[37] The recommendation to consider octreotide in patients with large tumor burden or progressive disease is based on the results of the PROMID study, a placebo-controlled phase III trial of 85 patients with metastatic midgut neuroendocrine tumors. This showed median time to tumor progression of 14.3 and 6 months in the octreotide LAR and placebo groups, respectively (P = 0.000072).[34] After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group and in 37.2% of patients in the placebo group. Results of long-term survival of patients in the PROMID study were recently reported.[38] Median overall survival (OS) for was not significantly different at 84 months in the placebo arm and not reached in the octreotide arm [heart rate (HR) 0.85; 95% confidence interval (CI) 0.46-1.56; P = 0.59]. However, post-study treatment included octreotide in 38 of 43 patients in the placebo arm, possibily confounding interpretation of long-term survival results. Currently, the maximum Food and Drug Administration-approved dosage and administration of octreotide long-acting repeatable (LAR), indicated for severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and VIPomas, is 30 mg every 4 weeks.[39] A recent physician expert consensus panel highlighted the appropriateness of using standard dose SSAs for control of hormonal symptoms and tumor growth in patients with advanced carcinoid tumors, as well as increasing dose/frequency of SSAs in treatment of refractory carcinoid syndrome.[33] The panel also recommended that increase in the dose/frequency of SSAs be considered for patients with radiographic progression, particularly in cases where disease was previously stabilized at a lower dose.

LANREOTIDE

Lanreotide (BIM 23014) has a similar mechanism of action as octreotide, also displaying high-affinity binding for types 2 and 5 receptors, low affinity for types 1 and 4, and medium affinity for type 3.[17] Lanreotide is a long-acting SSA analog administred every 10-14 days and has a similar efficacy to octreotide in the treatment of NETs. Studies have shown it to be effective at controlling symptoms in patients with carcinoid tumors, gastrinomas, and vasoactive intestinal peptide tumors (VIPomas).[40-42] A new slow-release depot preparation of lanreotide, "Lanreotide Autogel" administered subcutaneously at a dose of 60, 90, or 120 mg once a month was thereafter produced. The international phase III ELECT trial randomized 115 patients with carcinoid syndrome who were either naive to or responsive to octreotide to receive 120 mg of lanreotide or placebo.[43] Although the pre-defined difference in percentage of days the patients used rescue octreotide was not met, the panel believes that the difference seen (34% in the lanreotide arm *vs.* 49% in the placebo arm; P = 0.02) was significant enough to warrant use of lanreotide for symptom control. The recommendation that lanreotide be considered for control of tumor growth in patients with clinically significant tumor burden or progressive disease is based on results of the CLARINET study. The CLARINET study randomized 204 patients with locally advanced or metastatic non-functioning pancreatic or intestinal neuroendocrine tumors to receive either lanreotide or placebo and followed patients for progression-free survival (PFS). Results showed that treatment with lanreotide for 2 years resulted in an improvement in PFS over placebo (PFS not reached *vs.* 18 months; HR 0.47; 95% CI 0.30-0.73; $P < 0.001$).[44]

No clear consensus exists on the timing of octreotide or lanreotide initiation in asymptomatic patients with metastatic neuroendocrine tumors and low tumor burden. Although initiation of octreotide or lanreotide can be considered in these patients, deferring initiation until evidence of tumor progression is seen may also be appropriate in selected patients (National Comprehensive Cancer Network Guideline 2015).

PASIREOTIDE

Pasireotide (SOM 230) has high affinity for SSTR1, 2, 3, and 5, and displays a 30- to 40-fold higher affinity for SSTR1 and SSTR5 than octreotide or lanreotide.[45] Octreotide and Lanreotide have been used to treat acromegaly successfully because 90% of GH-secreting pituitary tumours express SSTR2 and SSTR5. However, given that pasireotide has 40-fold higher affinity and a 158-fold higher functional activity for SSTR5 than octreotide, pasireotide may be more effective than octreotide in acromegaly.[46] In phase II clinical trials, pasireotide has been demonstrated to inhibit GH secretion from pituitary tumours, control symptoms of the carcinoid syndrome associated with metastatic NETs, and inhibit ACTH secretion in Cushing's Disease.[47]

CHEMOTHERAPY

NENs usually arise as advanced and of low/intermediate grade and only in a minority of cases as high grade.[48] Prognosis depends on the histological differentiation, staging, and grade.[49-51] Most are non-functioning and metastatic at diagnosis.[52] Gastro-entero-pancreatic NENs

(GEP NETs) are classified on the basis of their proliferation rate as assessed by either mitotic index (MI) and/or nuclear Ki67 (WHO 2010).[53] Low-grade or G1 are those with 0-2% Ki67 and/or < 2 MI per 10 high power fields (HPF), intermediate-grade or G2 those with 3-20% Ki67 and/or 2-20 MI per 10 HPF, high-grade or G3 those with > 20% Ki67 and/or > 20 MI per 10 HPF. G1 and G2 are called neuroendocrine tumors (NETs) and G3 neuroendocrine carcinomas (NECs). This terminology is only valid for GEP NETs. According to the WHO classification (2004),[54] lung NETs are classified as: typical carcinoids, with < 2 mitoses per 10 HPF and lacking necrosis; atypical carcinoids, with 2-10 mitoses per 10 HPF and/or punctate necrosis; large cell neuroendocrine carcinomas, with > 10 mitoses per 10 HPF (median 70), coarse nuclear chromatin and extensive necrosis; and small cell carcinomas with > 10 mitoses per 10 HPF (median 80), even chromatin and extensive necrosis. Therapeutic options include local treatments such as surgery, as well as interventional radiology and systemic treatments, such as chemotherapy, SSAs, interferon α2b, peptide receptor radionuclide therapy and, as only for pancreatic NETs, molecular targeted agents including everolimus and sunitinib.

Chemotherapy in neuroendocrine carcinomas

Chemotherapy is the most common treatment approach in advanced NECs. Although these neoplasms appear relatively chemosensitive their prognosis is dismail. Cisplatin [Compound Danshen Dripping Pills (CDDP)]/ etoposide [vepeside-16 (VP-16)] is the most often proposed regimen chemotherapy based on the assumption that the clinical behavior of NECs is similar to that of lung small cell carcinomas. The literature, however, is rather scant in this regard and is limited to studies rather dated. In 1991, Moertel *et al*.[55] treated 45 metastatic NENs patients, 14 of which derived from GEP tract. The regimen consisted of VP-16 130 mg/m^2 per day for 3 days and CDDP 45 mg/m^2 per day for 2 days, on days 2 and 3, every 3 weeks. Only 18 patients had a NEC. The rate of objective tumor responses was clearly different between NECs (67%) and NETs (7%). In NECs the time to tumor progression (TTP) was 11 months and OS 19 months, reflecting a still unfavorable prognosis. Since then, CDDP/VP-16 has been considered the standard regimen in NEC.[55] In 1999, in a retrospective French analysis, 53 patients with advanced NENs received CDDP 100 mg/m^2 per day + VP-16 100 mg/m^2 per day for 3 days, every 3 weeks. Forty-one patients had NEC and 20 a neoplasm arising from the GEP tract (13 pancreatic). This was first-line chemotherapy in 70% of NEC. The response rate, once again, was clearly different between NECs (42%) and NETs (9%). Median PFS survival was 9 months in NECs and 2 months in NETs. However, OS was 15 months in NECs and 18 months in NETs.[56] A third study included 36 patients with advanced NEN of which only 9 were NECs, while the remaining 27 NENs were included only due to their rapid clinical progression. The regimen was VP-16 100 mg/m^2 per day for 3 days + CDDP 45 mg/m^2 per day for 2 days, every 4 weeks. Response rate (RR) was similar between NECs (40%) and NETs (33%).[57] In a more recent Eastern retrospective analysis, 21 untreated patients with NECs of hepato-biliary-pancreatic tract (with 10 pancreatic NECs), CDDP was administered at 80 mg/m^2 day 1 and VP-16 at 100 mg/m^2 per day for 3 days, every 3 weeks. RR was 14%, but with a short PFS (1.8 months) and OS (5.8 months) and high toxicity.[58] To date, some questions still remain: first, the potential role of alternative regimens to platinum-based chemotherapy, and then the homogeneity of the category of NECs in terms of biological aggressiveness and chemosensitivity. About any alternative regimens, the experts have suggested that carboplatin instead of cisplatin or irinotecan instead of etoposide are acceptable options for extrapulmonary NECs.[18] This is based on data from small cell lung cancer rather than experiences in the NECs, although in a recent Scandinavian retrospective analysis of over 200 patients with advanced GEP NECs treated with chemotherapy, the platinum-based regimens (particularly cisplatin versus carboplatin) did not influence the response and survival in a statistically significant way.[19] In this analysis the patients with Ki67 < 55% were less responsive (15% *vs.* 42%; $P = 0.001$) but lived longer (14 *vs.* 10 months; $P < 0.001$) than those with Ki67 > 55 %. On this basis, in patients with NEC and Ki67 < 55% it is possible to consider alternative chemotherapy regimens than those which are platinum-based. Such observations, while respecting the existing classifications, could be a starting point for research to define, within the NECs group, a different category of neoplasms, less aggressive and that, therefore, could be treated in a different way from that usually proposed. A recent retrospective publication reported the results about the treatment with CDDP + Irinotecan in 16 patients with advanced GEP NECs. The response rate was 51%, median PFS 5.5 months, and OS 10.6 months.[59] A further subgroup of patients with GEP NENs G3 (WHO 2010) is represented by morphologically well-differentiated neuroendocrine neoplasms while having Ki67 > 20% and/or mitosis > 20/10 HPF. Recent reports suggest that these tumors have a better prognosis than other GEP NECs and are less responsive to conventional chemotherapies.[60,61] Second-line chemotherapy after platinum-containing regimens has not been well defined. Reports of literature are very scarce. FOLFIRI regimen was administered in a series of 19 patients with GEP NECs who had received platinum-based chemotherapy as first-line. Objective response rate (ORR) was 31% and tumor control was 62%.[62] In another published experience, temozolomide was used as second line, alone or in combination with capecitabine +/- bevacizumab. Response rate was 33%, with a median duration of 19 months, PFS 6 months and OS 22 months.[63]

Chemotherapy in neuroendocrine tumors

In NETs, chemotherapy may be considered in therapeutic strategy because it can contribute to tumor and symptom control by reducing extent of disease. Therapy based on a single-agent chemotherapy have shown ORR usually not

higher than 20%, and so these are generally reserved to chemonaïve patients when the clinical condition does not allow therapy with multiple agents. Poly-chemotherapy regimens have shown greater activity as evidenced by numerous phase II studies and retrospective analyses. Drugs with activity in this setting belong to the class of alkylating agents [streptozotocin dacarbazine (TMZ)], anti-metabolites (5-fluorouracil, capecitabine) and, more recently, oxaliplatin. Streptozotocin (STZ) is one of the drugs most commonly proposed in patients with pancreatic NETs (pNETs), but it is not marketed in Italy. It has been much criticized due to its toxicity, especially renal and because some studies have reported very high ORR but based on often questionable evaluation methods of response. The most reliable study[64] had 84 pNETs patients treated with a combination of 5-fluorouracil (5-FU), adriamicin, and STZ with a 39% partial response (PR) but 20% had moderate-to-severe toxicity, especially in terms of neutropenia and asthenia.

Dacarbazine has been used in a mixed population in Italy in combination with 5-FU and epirubycin with 30% partial response rate.[65] The same combination used in a mixed population of patients, predominantly pretreated, with low grade tumors and an intermediate proliferation index. The result was a good disease control and the demonstration that chemotherapy may also be active in patients with non pNETs, GEP, NETs, and non-GEP NETs.[20]

Recently, new combinations have been tested in phase II trials. Temozolomide is an alkylating agent used in NETs due to its oral use. There are some retrospective and prospective studies showing activity but, because of the small number of patients involved and the variety of regimens used, it is difficult to recommend the best regimen. Interesting results have emerged from a retrospective analysis published in 2011 in association with capecitabine in pNETs naïve for any type of chemotherapy.[66] The high response rate (70%) and low toxicity led to a prospective phase II study conducted in the US to validate this combination. Methylguanine-methyltransferase (MGMT) is an enzyme that acts by methylating oxygen in position 8 of guanine, allowing repair of damage induced on DNA and making the expression of the enzyme inversely proportional to the response to the TMZ itself. In a retrospective analysis of 97 patients with NETs (pancreatic, intestinal, lung carcinoid tumors) treated with TMZ, the authors showed that the lack of expression of MGMT is more common in pNETs than in carcinoids and demonstrated a partial response rate of 34% in pNETs and only 2% in carcinoids.[21] These observations suggest that the state of MGMT could be a potential predictor of response to alkylating agents in NETs and therefore that studies of MGMT in tumor tissue are needed.

As regards the platinum derivatives, in 2006 a clinical study conducted by Italian Trials in Medical Oncology[22] evaluated the combination of capecitabine and oxaliplatin on a group of heterogeneous NENs in terms of the site of primary tumor and biology (well differentiated, progressive on biotherapy, poorly differentiated). This study indicates that oxaliplatin may be effective, both in digestive NETs and extra-digestive, especially low-grade. The role of oxaliplatin was studied by another group[67] in a retrospective analysis of a heterogeneous population in terms of primary tumor, biology, and disease progression at baseline. All patients except one had a low-grade tumor according to 2000 WHO classification but Ki67 was only available in 4 of 20 patients. There was a RR of 84%, 7 months for PFS and 23 months for OS. More recently, another group explored the activity and toxicity of oxaliplatin-based chemotherapy in an Italian muticenter "real world" study. A heterogeneous population of 78 NENs with well-detailed tumour characterization was analyzed between 1999-2013 and found that an oxalipatin-based regimen to be active and well-tolerated, including in previously treated patients.[68]

Metronomic chemotherapy

The various way of chemotherapy administration currently represents an interesting issue. The NENs are highly vascularized neoplasms so angiogenesis plays a key role in the growth of these tumors. For this reason, metronomic chemotherapy, defined as continuous administration of a low-dose chemotherapeutic drug, could have an antiangiogenic-reducing effect. One group 5-FU with octreotide LAR, reaching 23 months TTP in patients with GEP NETs.[69] The same group has also shown that expression of thymidylate synthase, an enzyme involved in the metabolism of 5-FU, reduces time to progression (TTP) and OS in patients with GEP NETs treated with 5-FU.[70] A phase II single arm trial with metronomic capcitabine in combination with octreotide LAR and bevacizumab has been used in patients with intestinal NENs.[23] The study was conducted from 2006 to 2009 in 5 centers and included 45 patients with well/moderately differentiated, locally advanced or metastatic disease, from various origins. Some were chemonaive and were progressing on SSA or radioreceptor therapy. Metronomic capecitabine was administered at a fixed dose of 2,000 mg per day in combination with octreotide LAR 20 mg every 4 weeks and bevacizumab at 5 mg/kg, intravenously, every 2 weeks. There was a > 80% (PR + stable disease), especially in patients with GEP NENs, but when responses were analyzed for the primary tumor site a higher RR in patients with pancreatic neuroendocrine neoplasms (pNENs) was observed than those with extrapancreatic NENs. Temozolomide was used with a metronomic schedule as well. The dose was 100 mg daily continuously in combination with bevacizumab and octreotide LAR in a group of 15 patients with low-grade NEN (Ki67 < 20%) of various origins, functioning and non-functioning, and progressive on at least first-line therapy. Partial responses were 57% with 9 months TTP.[24] It is noteworthy that 47% of patients had pNEN and 67% had an NEN with Ki67 less than or equal to 5%. The authors conclude that the very

high RR suggested that prolonged administration of TMZ can induce a depletion of MGMT in favor of TMZ itself. Despite study limitations (small number, heterogeneity), the high RR suggests the need to investigate this schedule in a more homogeneous population (as for primary tumor site and biological characteristics) in order to confirm the effectiveness of TMZ based-chemotherapy and validate the predictive role of MGMT.

Chemotherapy in thoracic NETs

Due to their rarity, thoracic NENs (typical and atypical carcinoids) are usually included in studies with chemotherapy designed for NENs derived from other anatomical regions. Thus, there is no standard chemotherapy regimen for thoracic NENs and any therapeutic results do not appear homogeneous. Moreover, given their low proliferative activity, carcinoids are generally considered to be chemo-resistant.[71] Single-agent chemotherapy has shown no more than 20% overall ORR, so mono-chemotherapy is suggested for pretreated patients or patients with poor performance status or severe comorbidities. Older phase II or III trials have been published but they were not considered homogeneous in terms of population and response evaluation criteria due to poorly definition. The drugs mostly used as single-agent are 5-FU, CDDP, carboplatin, irinotecan, TMZ, gemcitabine, VP-16, doxorubicin, STZ, dacarbazine, paclitaxel, docetaxel, and pemetrexed. Poly-chemotherapy is able to produce a radiological PR in only 5-10% of patients, but with symptomatic responses in 40-60% of cases. However, these results are extrapolated from studies including patients with NENs derived from any anatomical site, reducing the levels of trial evidence, even for well-conducted study, and with low probability of bias. A specific study of bronchial carcinoids was recently published[72] that examined TMZ as monotherapy in 31 progressive metastatic bronchial carcinoid patients. The treatment was active, showing 66% ORR, and well tolerated. However, combining regimens with other agents should be further studied.

CONCLUSION

In conclusion, many drugs have shown activity but many questions still remain: which drugs to use, which schedule, timing and, above all, which predictors can guide clinicians in the choice of chemotherapy. Despite the complexity and the heterogeneity of these tumors, the main challenge in the near future will be to design clinical trials that will answer these questions. It is also very important that the therapeutic decision only be achieved as part of a multidisciplinary program.

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Patient consent

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Ethics approval

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