Targeted Therapies for Neuroendocrine Neoplasms

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Introduction

Neuroendocrine tumors (NETs) are neoplasms that arise in the diffuse neuroendocrine system and are characterized by the ability to synthesize, store, and secrete a variety of neuroamines and peptides [11]. They commonly originate in the gastrointestinal tract and bronchopulmonary system. NETs comprise a spectrum of diseases ranging from well-differentiated, low-grade tumors to poorly differentiated, high-grade carcinomas. Significant progress in the understanding of their molecular biology has been made in recent years. While most targeted therapies in this field have been developed empirically, knowledge of genomic landscape [2, 16] and signaling pathways has led to better understanding of their mechanisms of action. In this chapter, we describe the current available targeted therapies for neuroendocrine tumors as well as drugs in development.

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Somatostatin Receptor Pathway

Somatostatin Analogs

Somatostatin was initially identified as an inhibitor of growth hormone and was subsequently found to perform numerous other inhibitory functions within the diffuse endocrine system including suppression of other hormones such as gastrin, cholecystokinin, and serotonin. The human hormone somatostatin has two bioactive forms consisting of 14 and 28 amino acids [31]. It interacts with somatostatin receptors which belong to a family of G-protein coupled receptors [23]. The vast majority of differentiated NETs (over 80 %) express somatostatin receptors on their cell surface, thereby representing an attractive target for medical therapy. Five types of somatostatin receptors (SST1, SST2, SST3, SST4, and SST5) have been identified in NET cells [8]. Octreotide and lanreotide are both somatostatin analogs (SSA) that share similar somatostatin receptor affinity profiles, binding avidly to SST2 and moderately to SST5 [25]. Both drugs have been used to treat hormonal symptoms associated with NETs for decades.

The first clinical trial of octreotide evaluated the drug in 25 patients with malignant carcinoid syndrome [20]. This study showed significant improvement of flushing and diarrhea as well as major 5-HIAA reductions in urine in roughly 80 % of patients, leading to the approval of octreotide by the Food and Drug Administration (FDA) for management of the carcinoid syndrome. A subsequent crossover trial comparing octreotide versus lanreotide in 33 patients with carcinoid syndrome demonstrated similar symptom control and biochemical responses between the two analogs [26]. Additional trials have also demonstrated that both SSAs can palliate hormonal syndromes associated with functioning pancreatic NETs, particularly VIPomas and glucagonomas [24].

In recent years, high-level evidence has emerged that SSAs can significantly inhibit growth of well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [36]. The antiproliferative effect of SSAs can be divided into two categories: “direct” and “indirect”. The direct effect involves interaction between SSAs and somatostatin receptors on tumor cells. Although the precise signaling transduction pathways are not fully understood, the initial steps appear to involve activation of phosphotyrosine phosphatases (PTPs) and modulation of the MAP-kinase pathway [30]. The indirect antiproliferative effect is mediated through suppression of circulating growth factors such as vascular-endothelial growth factor (VEGF) and insulin-like growth factor (IGF) [41].

The PROMID study [32] was a randomized phase III trial that compared octreotide LAR 30 mg versus placebo in 85 patients with advanced carcinoid tumors originating in the midgut. Time to tumor progression (TTP) increased from 6 months in the placebo arm to 14.3 months in the octreotide LAR arm ($p = 0.000072$). A subgroup analysis showed that patients with low tumor burden (<10 % hepatic involvement) and resected primary tumors benefitted most significantly from treatment with octreotide LAR. There was no significant difference in the adverse effects

profiles of both arms. The results were seen with caution as some felt that the early termination of the study after an interim analysis could have overestimated the benefit of octreotide LAR. However, the CLARINET study [3] confirmed the antiproliferative effects of SSAs. This randomized phase III study compared depot-lanreotide 120 mg to placebo in 204 patients with hormonally nonfunctioning GEP-NETs. A 53 % improvement in progression free survival (PFS) was seen with lanreotide (hazard ratio 0.47, 95 % CI: 0.30–0.73; $p = 0.0002$), meeting the trial's primary endpoint. The most common adverse effects associated with lanreotide were diarrhea, abdominal pain, and cholelithiasis. While both octreotide and lanreotide inhibit tumor growth in a clinically and statistically significant fashion, objective responses with both somatostatin analogs are exceptionally rare.

Pasireotide is a newer SSA that was developed with a particularly strong binding affinity to SST5, SST1, and SST3. It is still unclear whether this enhanced binding affinity results in improved clinical outcomes. While a phase II study of pasireotide in patients with refractory carcinoid syndrome demonstrated symptom improvement in 27 % of patients [21], a randomized phase III trial comparing pasireotide to octreotide LAR 40 mg in patients with poor symptom control showed no difference in palliation of flushing and diarrhea [42]. A phase II clinical trial of pasireotide in a heterogeneous population of treatment-naïve NET patients demonstrated a median PFS of 11 months [6]. Pasireotide is associated with a high rate of hyperglycemia due to binding of SST5. Its future development in NETs is uncertain.

Peptide Receptor Radionuclide Therapy

The use of radiolabeled somatostatin analogs is another promising option to target NETs that express high levels of somatostatin receptors. In addition to being used for diagnostic purposes, they can be used to deliver therapeutic radiation directly to tumor cells. Radiolabeled somatostatin analogs consist of three parts: a cyclic octapeptide, a chelator, and a radionuclide. Several variants of such conjugates have been developed, with indium-111 (^{111}In), yttrium-90 (^{90}Y), and lutetium-177 (^{177}Lu) being the most comprehensively evaluated [22].

The initial studies of Peptide Receptor Radionuclide Therapy (PRPT) used ^{111}In, but the characteristics of ^{111}In as a radionuclide were not optimal for the management of NETs. Currently, the most commonly used isotopes are ^{90}Y and ^{177}Lu, but no randomized trials have been performed comparing those two radionuclides. The reported radiographic response rates range from 4 to 47 %, with much of the heterogeneity in response rates likely relating to primary tumor site as well as line of therapy [22, 40]. Overall, PRRT is well tolerated, seems to significantly slow progression, and is associated with relatively few serious adverse events. Rates of renal insufficiency are low when prophylactic amino acids are infused. Long-term bone marrow toxicity, including myelodysplastic syndrome and acute leukemia, appears to occur in roughly 1 % of treated patients. Despite its common use in Europe in a quasi-investigational basis, PRRT has not been approved for use in the USA. The

NETTER-1 study is the first phase III multicentric, randomized, controlled, parallel-group study, comparing ^{177}Lu-DOTATATE with Octreotide LAR. In this study, treatment with PRRT plus best supportive care (30 mg Octreotide LAR) is compared to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable and progressive somatostatin receptor positive midgut carcinoid tumors (ClinicalTrials.gov Identifier: NCT01578239). Results of the NETTER-1 will hopefully shed further light on the role of PRRT in the management of NETs.

mTOR Pathway

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that is currently the focus of intense interest because it integrates signals from growth factors, G protein-coupled receptor (GPCR) agonists, nutrients (amino acids and glucose), cellular energy levels (AMP/ATP ratio), and stress conditions to determine whether a cell proceeds to grow and divide [43]. Therefore it is a key module in the regulation of metabolism, migration, survival, autophagy, and growth [33].

Germline mutations of *TSC2*, an endogenous inhibitor of mTOR, are a risk factor for the development of pancreatic NETs. Somatic mutations in mTOR pathway genes, including *PTEN*, *PIK3CA*, and *TSC2* occur in roughly 15 % of pancreatic NETs [16]. Other alterations in mTOR pathway genes, including amplifications of *AKT1/2*, are observed in nearly one-third of small bowel carcinoid tumors [2].

Several inhibitors of mTOR have been developed and evaluated for the treatment of NETS, including the so-called rapalogs, temsirolimus and everolimus.

Everolimus

The oral mTOR inhibitor everolimus has been studied extensively in GEP-NETs. A phase II study, known as the RADIANT-1 trial, of 160 patients with pancreatic NETs investigated everolimus monotherapy ($N=115$) or everolimus plus octreotide ($N=45$) [46]. Response rates and median PFS were 9 % and 9.7 months with monotherapy versus 4 % and 16.7 months with combination therapy. A subsequent phase III study (RADIANT-2 trial) randomly assigned 429 patients with hormonally functional carcinoid tumors to treatment with everolimus 10 mg plus octreotide versus placebo plus octreotide. On central radiographic review, median PFS increased from 11.3 months on the placebo arm to 16.4 months on the everolimus arm (HR 0.77; $p=0.026$) [27]. While clinically significant, the primary endpoint fell short of its prespecified statistical significance threshold of $p<0.0246$. A potential explanation for the lack of statistical significance was the discrepancy between central versus local radiographic

review. There was no trend towards improvement in overall survival in the everolimus arm, possibly due to the high rate of crossover to everolimus in the placebo arm.

Another phase III study (RADIANT-3 trial) randomly assigned 410 patients with low- and intermediate-grade pancreatic NETs to treatment with everolimus 10 mg versus placebo [48]. Concurrent SSA therapy was allowed. Despite an objective response rate of only 5 % in the everolimus arm, the study demonstrated a clinically and statistically significant improvement in PFS. Median PFS increased from 4.6 months on the placebo arm to 11 months on the everolimus arm (HR 0.35, $p < 0.001$). Median overall survival was not reached and no statistically significant survival difference between the groups was observed; however, updated survival data has demonstrated a trend towards improvement with everolimus. Everolimus has since been approved by the FDA for treatment of patients with advanced pancreatic NETs.

To possibly expand the role of everolimus in NETs, the RADIANT-4 trial was designed to enroll patients with hormonally nonfunctioning carcinoid tumors. In this phase III study, 285 adults with histologically confirmed well-differentiated advanced NET of GI or lung origin, with no history of symptoms related to carcinoid syndrome were randomized to receive everolimus versus placebo with no crossover upon progression. Results are expected to be presented soon (ClinicalTrials.gov Identifier: NCT01524783). Also, multiple trials are ongoing to examine the use of everolimus in combination with various other agents. Examples of combinatory therapies under investigation include everolimus in addition to pasireotide, bevacizumab, erlotinib, cixutumumab, vatalanib, and several cytotoxic agents.

In general, side effects of everolimus include aphthous oral ulcers, rash, diarrhea, hyperglycemia, and cytopenias. Pneumonitis is a relatively rare but potentially serious toxicity that can be managed with dose reductions or interruptions and glucocorticoid therapy in symptomatic patients. Everolimus is an immunosuppressive drug, and atypical infections such as tuberculosis or aspergillosis are occasionally observed. While most toxicities are mild, chronic side effects may adversely impact patients' quality of life.

Temsirolimus

A phase II trial of temsirolimus in 37 patients with advanced NETs showed limited objective response as monotherapy [9]. Given the relatively modest activity of single-agent mTOR inhibitors in NETs, there is interest in developing novel combinatory treatment strategies. Hobday et al. [14] published results from a multicenter trial of temsirolimus and bevacizumab in 56 patients with progressive pancreatic NETs. Response rate (RR) was 41 % (23 of 56 patients) and median PFS was 13.2 months (95 % CI, 11.2–16.6). Median overall survival was 34 months (95 % CI, 27.1 to not reached). The most common grade 3 to 4 adverse events attributed to

therapy were hypertension (21 %), fatigue (16 %), lymphopenia (14 %), and hyperglycemia (14 %). This study suggested that the combination of temsirolimus and bevacizumab had substantial activity and reasonable tolerability.

VEGF Pathway

Neuroendocrine tumors are highly vascular and frequently express the vascular-endothelial growth factor (VEGF) ligand and receptor (VEGFR) [34, 38, 47]. Increased levels of circulating VEGF have been associated with tumor progression. Consequently, inhibition of the VEGF pathway has been identified as a therapeutic strategy. The VEGF pathway can be targeted by circulating VEGF inhibitors such as bevacizumab or with the use of multitargeted tyrosine kinase inhibitors against VEGFR, including sunitinib, pazopanib, and sorafenib.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that binds to circulating VEGF-A. In a randomized phase II trial, 44 patients with metastatic carcinoid tumors were randomly assigned to treatment with bevacizumab or pegylated interferon (PEG-IFN) for 18 weeks, followed by both agents in combination [47]. At the week 18 time point, the rate of PFS was 95 % on the bevacizumab arm versus 68 % on the PEG-IFN arm. On functional CT scans performed at baseline and on day 2 of therapy, bevacizumab treatment caused average reductions in tumor blood flow of 49 %. Despite this promising phase II data, a randomized phase III trial sponsored by the Southwest Oncology Group (SWOG) failed to show a significant difference in PFS comparing bevacizumab to IFN-alpha in carcinoid tumor patients with high risk prognostic features. In this study of 427 patients, median PFS was 16.6 months in the bevacizumab arm and 15.4 months with the IFN arm ($p = 0.55$) [44].

Combinations of bevacizumab and other agents are also under investigation, with several phase II trials reporting promising data. In one study, the combination of bevacizumab plus temozolomide was shown to be effective in patients with advanced NET, particularly in the subgroup of pancreatic NETs [5]. In a small phase II study of 31 evaluable patients, a combined regimen of bevacizumab plus capecitabine and oxaliplatin resulted in PR in 23 % and SD in 71 % [19]. Of particular note, 6 of 7 patients with pancreatic NET had PR. Overall, the 1-year PFS with this treatment combination was 52 % and median PFS was 13.7 months. The combination of bevacizumab and FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin) has also been evaluated in a small study of patients with NET [39]. Two of 6 patients with pancreatic NET had PR compared with 1 of 5 patients with small-bowel (carcinoid) NET, whereas SD was observed in the majority of patients regardless of

primary site. A bevacizumab/everolimus combination has also demonstrated promising early results. In a small, randomized run-in study of 39 patients with low- to intermediate-grade NET, 26 % experienced PR and 67 % had SD [45].

A randomized phase II study of everolimus plus bevacizumab versus everolimus monotherapy demonstrated improvement response rates in the combination group (31 % versus 12 %) and PFS (16.7 months versus 14.0 months; $p = 0.12$) [17].

Sunitinib

Sunitinib is a tyrosine kinase inhibitor (TKI) that targets VEGFR1, -2, and -3, as well as platelet-derived growth factor receptor (PDGFR). This drug showed promising results in a subgroup of patients with pancreatic NETs in a phase II trial [18]. Therefore, a multinational randomized phase III trial comparing sunitinib 37.5 mg/day versus placebo in 171 patients with low- and intermediate-grade pancreatic NETs was conducted. There was a statistically significant improvement in median PFS from 5.5 months on the placebo arm to 11.1 months on the sunitinib arm ($p < 0.001$) [29]. A trend towards improvement in overall survival was also noted but was not statistically significant. The objective response rate associated with sunitinib was 9.3 %. Side effects of sunitinib included nausea, diarrhea, fatigue, cytopenias, palmar-plantar erythrodysesthesia, and hypertension. Based on the results of this study, sunitinib is FDA approved for treatment of pancreatic NETs.

Sorafenib

Sorafenib is a small-molecule TKI that inhibits both intracellular and cell surface kinases (BRAF, CRAF, KIT, FLT-3, RET, VEGFR1, VEGFR2, VEGFR3, and PDGFRβ) [10]. This drug, which was initially approved by the FDA in the USA for the treatment of renal cell carcinoma, has shown modest activity as single agent for the treatment of metastatic NETs [15]. The combination of sorafenib with bevacizumab was also tested [4]. Although it showed some clinical activity in patients with advanced NETs, the combination was associated with an unfavorable safety profile [4].

Other Inhibitors of VEGFR

Other VEGFR targeting TKIs, including pazopanib and axitinib, are being investigated in clinical trials of GEP-NET patients. A phase II study that included 70 patients with advanced pancreatic NETs and carcinoid tumors evaluated the

efficacy of pazopanib with octreotide LAR. No responses were seen in patients with carcinoid tumors and 21 % of pancreatic NETs patients achieved an objective response [28]. Another phase II trial showed clinical activity of pazopanib as a single agent in advanced NETs regardless of previous treatments [12]. Currently, a randomized phase II study is investigating pazopanib versus placebo in patients with advanced, progressive carcinoid tumors.

Additional Pathways

Epidermal growth factor receptor (EGFR), a transmembrane tyrosine kinase receptor, is activated when a ligand (EGF or related factors) binds to its extracellular domain. Activation of EGFR leads to downstream activation of three major signaling pathways including the Ras/Raf/MEK/ERK and the PI3K-Akt pathways [1]. Despite showing activity in NET cell lines [35], the use of EGFR inhibitors (gefitinib) did not result in significant clinical activity [13]. Preclinical data suggest that concomitant inhibition of two nonredundant amplified pathways (mTOR and EGFR) could reverse potential drug resistance and lead to tumor growth inhibition. Therefore, the efficacy of erlotinib, another EGFR inhibitor, is currently being assessed in a phase II study to evaluate the safety and efficacy of everolimus plus erlotinib in patients with well- to moderately-differentiated neuroendocrine tumors (ClinicalTrials.gov Identifier: NCT00843531).

It has been showed that IGF-1 receptor (IGF-1R) is overexpressed in NETs making it another attractive target for therapy. Preclinical data suggest multiple roles for the IGF-1R in NETs, including mediation of resistance to mTOR inhibitors. Cixutumumab, a monoclonal antibody (MAB) against IGF-1R, was tested in combination with everolimus and octreotide in patients with well-differentiated NET, but results have been disappointing [7]. Ganitumab, another human MAB against IGF-1R, was tested in metastatic low- and intermediate-grade carcinoids or pNETs. Although well tolerated, treatment with single-agent ganitumab failed to result in significant tumor responses among patients with metastatic well-differentiated carcinoid or pancreatic NET [37]. Histone deacetylase inhibitors, proteasome inhibitors, and c-Kit and PDGFR inhibitors have been also tested.

Conclusions

Somatostatin analogs continue to represent the primary first-line treatment for most well-differentiated metastatic NETs due to their antisecretory and antiproliferative activity combined with a tolerable side effect profile. In recent years, new targeted therapies, including mTOR inhibitors and VEGF inhibitors, have been approved for treatment of pancreatic NETs. Their scope may also expand to treatment of advanced

carcinoid tumors based on results of recent clinical trials, including the RADIANT-4 study. Radiolabeled somatostatin analogs may also be approved for somatostatin-receptor-expressing tumors' pending results of the NETTER study. Appropriate selection and sequencing of therapies will be the focus of future trials.

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