9 New Approaches in Medical Therapies

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9.1 Introduction

Advances in research of the molecular pathways associated with NETs have led to the discovery of multiple treatment options for patients with advanced NETs. Current available therapies include somatostatin analogs (SSA), peptide receptor radionuclide therapy (PRRT), the mammalian target of rapamycin (mTOR) inhibitor everolimus, and the tyrosine kinase inhibitor (TKi) sunitinib and interferon. Moreover, cytotoxic agents are indicated for the treatment of aggressive well-differentiated NETs and of poorly differentiated neuroendocrine carcinomas. Hepatic-directed treatments are recommended for patients with well-differentiated NETs and liver-predominant disease.

However, different drugs are currently under investigation in NET therapy, some molecules are similar to drugs already used in clinical practice, while others are approved in other tumors but not in NETs.

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9.2 Pasireotide

Pasireotide is a newer SSA with higher affinity for all subtypes of somatostatin receptors (SSTRs) 1, 2, 3, and 5, compared to octreotide and lanreotide, which mainly target SSTR2.

Pasireotide showed to be effective and well tolerated in controlling diarrhea and flushing related to carcinoid syndrome in patients with advanced NET refractory or resistant to octreotide LAR therapy [1]. However, pasireotide did not show a difference in symptoms control at 6 months in a randomized phase III trial compared to octreotide LAR, therefore, the study was interrupted early despite initial PFS improvements noted in the pasireotide treatment arm [2].

The phase II randomized trial, LUNA trial, assessed the efficacy of pasireotide alone or in combination with everolimus in lung and thymic carcinoids. The combination therapy with pasireotide and everolimus was not superior in mPFS compared to everolimus alone (12.5 months in the everolimus group and 11.8 months in the combination group), while a higher rate of adverse events was reported in combination group [3]. Several other monotherapy, combination, or increased dosage treatment strategies with pasireotide are currently being explored [4]. Pasireotide has not been approved for use in GEP-NETs but is certainly a focus of future research (Fig. 9.1).

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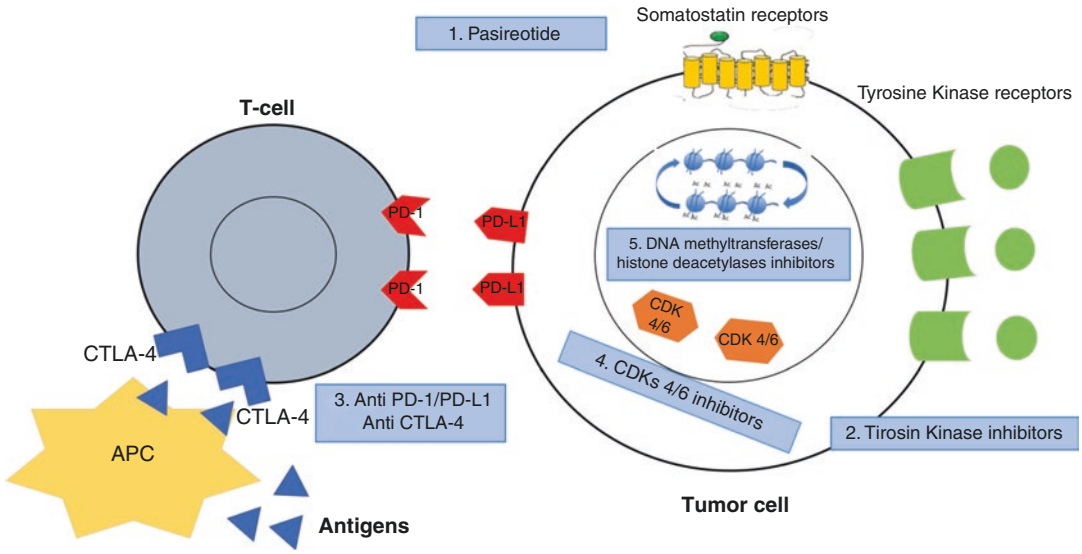

Fig. 9.1 Overview of new therapeutic strategies for NETs. *APC* antigen-presenting cell, *CTLA-4* cytotoxic T lymphocyte-associated protein-4, *PD-1* programmed cell death-1, *CDK 4/6* cyclin-dependent kinases

9.3 New Tyrosine Kinase Inhibitors

Neuroendocrine neoplasms are conventionally considered highly vascularized tumors, especially well-differentiated tumors that showed a high microvascular density [5, 6]. Tyrosine kinase pathways are involved in angiogenesis, tumor growth, and progression. For that reason, several molecules that act on specific tergets such as VEGFR, PDGFR, c-KIT, Flt-3, and RET [7] are under investigation.

Sunitinib is the only available TKi approved in PanNETs [8]. Clinical studies investigated other TKi with different activities on the multiple tyrosine kinase receptors (VEGFR, PDGFR, FGFR, KIT, RET, and MET).

Pazopanib is an oral multi-TKi that targets VRGFR1-2-3, PDGFR, c-Kit, and FGFR 1-2-3. Three phase II trials analyzed the activity and safety of pazopanib in advanced well-differentiated NETs from different primary tumors.

The study by Phan et al. explored the efficacy of pazopanib 800 mg/day and octreotide LAR (up to 40 mg every 3 weeks) in 44 patients with metastatic or locally advanced G1-G2 well-differentiated tumors from mixed primary sites. Thirty-two patients had pancreatic NETs. A partial response was observed in 22% of patients with a median PFS of 14.4 months and a median OS of 25 months [9]. Another study by Ahn et al. investigated the efficacy and safety of pazopanib 800/day in 37 patients with metastatic G1-G2 well-differentiated NETs and poorly differentiated G3 NECs from pancreatic and colorectal primaries. A PR rate of 19%, SD 57%, and mPFS of 9 months were observed [10]. In this study, patients had not been previously treated with other TKi or everolimus. On the contrary, PAZONET trial included patients after at least one prior systemic therapy, including other TKis. The study enrolled 44 patients with advanced well-differentiated G1-G2 NETs, and the median PFS was 9.5 months for the whole population, but it should be noticed that it was 12.4 months for patients pretreated with TKi and 6.8 for patients pretreated with mTOR inhibitors [11].

However, no phase III randomized clinical trials have been performed to date that define the role of pazopanib in the management of NENs, therefore, it is not currently approved for the treatment, although it could be useful in tumors resistant to standard therapy.

In general, pazopanib was well tolerated; the most common side effects were fatigue, nausea,

diarrhea, and hypertension and the most severe reactions (grade 4) being thromboembolism and hypertriglyceridemia that occurred in one patient each [10].

Cabozantinib is an orally available TKi that exerts a strong antagonist activity against MET and VEGFR2, but it also targets several kinases implicated in tumor pathology as KIT, RET, AXL, TIE2, and FLT3 [12].

A single-arm phase II trial in advanced well-differentiated pancreatic and small intestine NET showed that cabozantinib improved median PFS (21.8 and 31.4 months) for both PNET as well as small intestine NETs [13]. These results have led to a phase III trial (CABINET) that is now ongoing in USA, to assess the efficacy of cabozantinib in patients with advanced well-differentiated NETs who have progressed on everolimus (NCT03375320), but at the moment, this treatment is not currently approved for use in GEP-NETs. Main toxicities associated to cabozantinib therapy were hypertension, hypophosphatemia, and diarrhea.

Lenvatinib is an oral TKi that targets VEGFR 1–3, PDGFR, FGFR, RET, and SCFR. The effect of lenvatinib 24 mg/day has been investigated in a phase II trial, TALENT trial, in patients with G1-G2 advanced pancreatic (55 patients) and gastrointestinal (56 patients) NETs. Among patients with pancreatic primary tumors, 64% and 25% of patients were pretreated with everolimus or sunitinib, respectively. The study reported an overall response rate of 29%, in particular 42.3% for pancreatic primaries and 16.3% for gastrointestinal primaries. Median PFS and OS were 15.5 months and 29.2 months for pancreatic and gastrointestinal NETs, respectively. The most frequent grade 3/4 adverse events were hypertension, fatigue, and diarrhea, and in this study, almost 90% of patients experienced an adverse event.

Axitinib is an oral, second generation TKi that targets VEGFR 1-2-3, PDGFR, and c-KIT.

Axitinib has been studied at the dose of 10 mg/day in a phase II trial in 30 patients with well-differentiated advanced extrapancreatic (gastrointestinal, thoracic, and unknown primary) NETs. Interestingly, 53% of patients had history of carcinoid syndrome. Median PFS was 26.7 months and median OS was 45.3 months. Adverse events were mainly hypertension, thyroid dysfunction, and thromboembolism [14]. On the basis of this phase II trial, a phase II/III placebo-controlled trial is ongoing to evaluate the effectiveness of axitinib associated to octreotide LAR vs. placebo associated to octreotide LAR in G1-G2 NETs from extrapancreatic primary (NCT01744249).

Surufatinib is TKi that not only inhibits VEGFR1-2-3 but also targets FGFR1 and CSF pathways, which represent the supposed main acquired mechanism of resistance to anti-VEGF therapies. A phase I/II trial studied the efficacy of surufatinib in 81 patients, 42 with pancreatic, and 39 with extrapancreatic NETs. Overall response rate was 19% and 15%, while median PFS was 21.2 months and 13.4 months, in pancreatic and extrapancreatic NET, respectively. Grade 3/4 adverse events were mainly hypertension, proteinuria, and hyperuricemia. On this basis, the research with surufatinib moved to a next step and surufatinib demostrated efficacy vesrus placebo in two phase III trials in Asia in extra-pancreatic NETs (SANET-p) and pancreatic NETs (SANET-p) (Xu J et al. Lancet Oncol 2020) conducted in Asia [15]. Therefore it is not available yet in Western Countries for the treatment of pancreatic and extra-pancreatic NETs.

9.4 Immune Checkpoint Inhibitors

A new modality of immunotherapy has recently modified cancer treatment approach and has changed the treatment of some cancers, such as melanoma and lung cancer. However, the application of checkpoint inhibitors in the management of patients with NETs is still evolving. Many factors have been proposed as potential predictor of response to immune checkpoint inhibitors as programmed cell death-1 ligand (PD-L1) expression, lymphocyte infiltration, mismatch repair deficiency, and consequently tumor mutational and neoantigen load.

Levels of PD-L1 vary widely across published studies, suggesting that expression of this protein is heterogeneous in G1/G2 NETs. In particular,

PD-L1 expression has been associated with more advanced tumors as well as intermediate- to high-grade (G2-G3) GEP-NETs [16]. Lymphocyte infiltration is commonly observed in these tumors, but considering the low proportion of cases positive for PD-1/PD-L1, it is not clear if TILs are effectively activated by tumor neoantigens. Moreover, mechanisms of mismatch repairs appear to be efficient in most NETs, consequently, the mutational burden of these malignancies is relatively low, as only 3% of panNETs harbor >17 mutations/Mb, a cutoff usually used to predict response to immunotherapy [17].

Microsatellite instability (MSI) is considered a predictive biomarker for response to PD-1/PD-L1 inhibition. In well-differentiated tumors, high-level MSI has been demonstrated in sporadic insulinomas [18], but rarely in other GEP-NETs [19–21].

Taking into account this data, well-differentiated NETs do not seem good candidates for immunotherapy. In contrast, it seems to be more likely that NECs could be a target to checkpoint immunotherapy, given their mutational load and dense immune infiltration [22].

Checkpoint inhibitors utilize antibodies to target the programmed cell death receptor 1 (PD)-1/PD-L1 or cytotoxic T lymphocyte antigen (CTLA)-4 inhibitory axis found on immune cells to lower their threshold for activation and generate a more robust antitumor response. Several PD-1/PD-L1 antibodies are available for clinical use including pembrolizumab, nivolumab, and avelumab as well as ipilimumab for CTLA4 targets [23].

Pembrolizumab, a monoclonal antibody (mAb) targeting PD-1, has been investigated in the phase Ib study KEYNOTE-028. Two hundred-seventeen patients had been evaluated for PD-1 expression and 36% were positive. The trial enrolled 16 and 25 patients with pretreated PD-L1-positive pancreatic and extrapancreatic (nine lungs and seven guts) NETs. Objective responses were observed in 12% of carcinoid cohort and 6% of pancreatic cohorts; SD rates were 60% and 88% in carcinoid and pancreatic cohort, respectively. The 1-year PFS rate was 27% for either subgroups. This study showed higher response rates in tumors that had high mutational burdens as well as microenvironments that were T cell-enriched suggesting potential criteria that will be helpful in predicting eligibility for these treatments [24].

These results have been confirmed by another study that has investigated the efficacy of pembrolizumab (KEYNOTE-158) in a larger cohort of patients (107 patients) with well-differentiated NETs of the lung and gastroenteropancreatic. Sixteen percent of patients had PD-L1-positive tumors. ORR was 3.7% with 4 PR and no complete response. Median PFS was 4.1 months and median OS was 24.2 months [25].

Similar results have been recently reported in a study of 116 patients with well-differentiated G1-G2 gastroenteropancreatic and lung NETs as well as gastroenteropancreatic poorly differentiated NECs treated with spartalizumab (PDR-001), a mAb anti-PD-1. In this study, ORR was 7.4% in well-differentiated NETs and 4.8% in poorly differentiated NEC, to be noted, patients with lung carcinoids had higher ORR (20%). Main grade 3/4 adverse events were abdominal and back pain, anemia, dyspnea, and hypertension. PD-L1 expression was generally low, GEP NEC patients had a higher proportion of PD-L1 expression (43%) [26].

A phase Ib trial investigated the efficacy of toripalimab, an mAb anti PD-1 receptor, in 40 patients with NENs with Ki-67 > 10% progressing to first-line therapy. ORR was 20% (eight partial response and six stable disease) and median disease objective response was 15.2 months [27].

One strategy to increase the percentage of response to immunotherapy is to combine two treatments.

The phase II basket trial (DART trial) explored the combination of ipilimumab and nivolumab in rare tumors. In the NEN cohort, 32 patients had a non-pancreatic NEN, 56% had a NEC. Most common primary sites were gastrointestinal (47%) and lung (19%). The overall ORR was 25%, but in patients with NEC, ORR was 44%. Median OS was 11 months. The most common toxicities were hypothyroidism, fatigue, and nausea [28]. It is currently unknown whether prior

treatment with chemotherapy or peptide receptor radiotherapy or concomitant treatment with TKi may enhance the efficacy of immunotherapy in NETs. Strategies to enhance immune response and efficacy of immunotherapy in NENs are based on modulation of T cells and reverse immunosuppression, in particular the association of two immune checkpoint inhibitors, or the association of immunotherapy with chemotherapy, PRRT, and target therapy is under evaluation in several clinical trials [29]. Checkpoint inhibitors are an exciting option that deserve further investigation.

9.5 Cyclin-Dependent 4/6 Inhibitors

The cyclin-dependent kinases (CDKs) regulating cell cycle progression have been viewed as promising targets for cancer therapy. Palbociclib is an inhibitor of CDK4 and CDK6 approved together with other third-generation CDK4/6 inhibitors (ribociclib and abemaciclib) for the treatment of hormone receptor-positive and HER2-negative breast cancer in combination with either aromatase inhibitors or fulvestrant based on significant improvements in PFS [30]. It shows a potent antiproliferative activity in RB-positive tumor cells in vitro, inducing G1 arrest [31–33] in pNET cell lines overexpressing CDK4 [34].

The phase I trial by Fujivara et al. with abemaciclib in 11 patients with advanced tumors with different primaries found a reduction in tumor size >30% in two patients, one of them with a NET [35].

This encouraging result has not been confirmed by the phase II trial by Grande et al. assessed activity and safety of palbociclib 125 mg 21 of 28 days in 21 patients with advanced or metastatic G1-G2 pancreatic neuroendocrine tumors. All patients received at least one line of previous therapy, and 66% of patients received more than two lines of therapy. The median PFS was only 2.6 months and there were no objective response. Fifty-four percent of patients showed a disease stabilization for more than 6 months. Main toxicities were muscle weakness, neutrophil, and platelet count decrease. No correlation between the clinical outcome and the expression of RB1, Ki-67, and p16 on the tumor tissue was observed [36]. Translational studies correlating palbociclib activity with Ki-67 proliferation index are ongoing.

9.6 Epigenetic Drugs

The low mutation rate observed in NET compared to other tumors suggests that other mechanisms, such as epigenetic changes, could be involved in NET development and progression.

The term epigenetics is referred to external modifications to DNA, which do not alter the DNA sequence but change chromatin structure influencing gene expression and genomic stability. Epigenetic changes are transmitted in cells divisions and consist of DNA methylation and histone modification. Both mechanisms are deregulated in cancer, including NET, and contribute to tumor evolution.

Epigenetic drugs inhibit proteins implicated in the writing, the reading, or the erasing of epigenetic marks such as DNA methylation or post-translational modifications of histones. The main categories of this compounds are the inhibitors of DNA methyltransferases, such as azacitidine and decitabine, and the inhibitors of histone deacetylases [37].

Methylation profiles can be a predictive factor of response to chemotherapeutic agents and of survival, as for example, the methylation of MGMT promoter. MGMT (O6-methylguanine-methyltransferase) is an enzyme of DNA repair, and the methylation of the promoter seems to predict for better response to therapy with alkylating agent as temozolomide in panNET patients [38, 39]. Larger and randomized clinical trials should be conducted to confirm these findings.

Studies in vitro in panNET and small intestine cell lines used DNA methylases inhibitor and histone deacetylases inhibitor, showing results in terms of reducing cell viability and increasing gene expression [40–44]. Interestingly, decitabine increased the expression of SSTR2 and the Ga-DOTATOC uptake in BON1 tumour-bearing

mice, indicating a possible therapy implication in reexpression of somatostatin receptors for PRRT [45, 46].

These drugs are under investigation also in clinical trials, and the efficacy in NETs is under investigation.

A phase II trial with panobinostat, a histone deacetylases inhibitor, has been conducted in 15 patients with metastatic, low-grade NETs. The study was stopped at planned interim analysis based on a Simon two-stage design. There were no radiologic responses, but all patients have a disease stabilization. The median PFS was 9.9 months, and the median OS was 47.3 months. Fatigue (27%), thrombocytopenia (20%), diarrhea (13%), and nausea (13%) were the most common related grade 3 toxicities. The low response rate and the mPFS did not meet the prespecified criteria to open the study to full accrual [46].

A phase I trial with CC90011, a reversible oral inhibitor of the epigenetic target, lysine-specific demethylase 1A (LSD 1) showed in 50 patients (26 with neuroendocrine neoplasms) a complete response in 1 patient and a disease stabilization in 22 patients, with 7 patients with a duration of >4 months(five bronchial and two prostate NENs). Toxicity were thrombocytopenia and neutropenia. Retrospective studies on the epigenetic profile of neuroendocrine tumors would be necessary for future researches and specific treatments. Currently, multiple clinical trials are underway attempting to identify and use biomarkers for clinical use (NCT02630654, NCT02948946).

Given the clinical heterogeneity observed in NETs based on grade, anatomical location, etc., it is imperative that future efforts work toward an improved molecular understanding of NETs and their response to particular treatments.

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