neoplasms.[79-80] IGF-1 receptors (IGF-1R), binding IGF-1, activate signals inside normal neuroendocrine cell, through components of the PI3K/Akt/mTOR and the Ras/Raf/MEK/ERK pathways,[82-86] inducing cellular proliferation and over-regulating antiapoptotic activity.[81] [Figure 1] IGF-1 receptors, then, are usually overexpressed in NETs,[87-90] especially in symptomatic and functioning ones. This represents a possible role in tumorigenesis of GEP and bronchial NETs and a potential target for therapy.[91-93] The rationale for the use of IGF1R inhibitors depends on their theoretical capability to reduce AKT phosphorylation induced by mTOR inhibitors.[94-96]

In this regard, cixutumumab, a fully human immunoglobulin G1 monoclonal antibody competitively binding IGF-1R, is in the early phases of clinical progress.[97] Cixutumumab is still studied in association with octreotide LAR in an ongoing phase II study enrolling patients with progressing metastatic P-NETs and midgut carcinoid tumors.[98] Also, the combination of cixutumumab, everolimus, and octreotide is being evaluated in a phase I trial conducted in patients with advanced low- or intermediate-grade neuroendocrine tumors for which standard curative measures do not exist (Clinical Trial: NCT01204476). Another similar phase I trial was performed in advanced cancer patients, with candidates receiving temsirolimus with cixutumumab. The preliminary results showed good tolerance.[99] [Table 3]

Similarly, ganitumumab, another fully human monoclonal antibody against IGF-1R, is undergoing evaluation in clinical trials. Rothenberg *et al*.[100] demonstrated encouraging activity and good tolerance in a phase I trial including previously treated metastatic NET patients [Table 3]. Strosberg *et al*.[101] performed a phase II study of ganitumumab in patients with metastatic progressive low- and intermediate-grade carcinoids or P-NETs. This trial showed a good tolerance of ganitumumab, but no objective responders [Table 3]. Further studies are necessary to deepen the role of cixutumumab and ganitumumab and to identify other IGF-1R targets.

VEGF AND ITS RECEPTOR INHIBITORS

Neuroendocrine neoplasms, especially for midgut and P-NETs and bronchial carcinoids, are highly vascularized and overexpress vascular endothelial growth factor (VEGF) and its receptors.[102,103] Four VEGF forms are individuated and examined: VEGF-A, VEGF-B, VEGF-C, and VEGF-D,[104-108] with a different affinity to their three own receptors.[109-113] [Figure 1] For these reasons, the interest of angiogenesis inhibition was encouraged.

The small molecule tyrosine kinase inhibitor (TKI) sunitinib has been studied as a targeted therapy option in NENs. Based on these results in term of response rate that were observed in phase I trial with sunitinib,[114,115] Kulke *et al*.[116] conducted a phase II trial evaluating the efficacy of sunitinib in GEP-NETs. They showed a significant antitumor activity in P-NETs *vs*. carcinoid tumors and good tolerance. In addition, in a phase III trial involving low- and intermediate-grade advanced P-NETs, Raymond *et al*.[117] demonstrated a better PFS in the arm of sunitinib compared to placebo. The improved PFS did not depend on previous treatments or concomitant SSAs. Therefore, sunitinib is approved for the treatment of P-NETs after disease progression.

Considering the importance of VEGF in the pathogenesis of NENs, bevacizumab, an anti-VEGF antibody, has been used either alone or in combination with other drugs with favorable results. A phase II trial, in particular, enrolled patients with advanced carcinoid tumors with stable doses of octreotide to receive either bevacizumab or pegylated Interferon α2b. Bevacizumab showed superiority in objective responses, reduction of tumor blood flow, and PFS.[118,119] Bevacizumab in association with temozolomide in patients with metastatic NETs also showed a major response rate, PFS, and OS in P-NETs.[120]

In another recently completed phase II study, everolimus and bevacizumab were shown to be associated with an overall tumor response rate of 26% and good tolerance in advanced P-NETs.[121] Therefore, a further phase II trial will compare everolimus alone with the combination of everolimus and bevacizumab in patients with P-NETs, in order to find supplementary function of antiangiogenetic agents in this setting of patients (ClinicalTrials. Gov Identifier: NCT01229943). Randomized studies of anti-VEGF TKI should also be evaluated in patients with advanced carcinoid tumors.

Pazopanib is an oral bioavailable, multitargeted tirosine kinase inhibitor (VEGF receptors 1, 2, and 3), involved in reducing neoplastic growth and dissemination.[122] Ahn *et al*.[123] demonstrated, in a non-randomized, open-labeled, single-center phase II trial, that pazopanib in monotherapy was as effective as the other available targeted therapies, not only in P-NETs, but also in GI NETs [Table 4]. Phan *et al*.[124,125] found that pazopanib in combination with octreotide LAR depot was more effective in advanced G1-G2 P-NETs than in advanced carcinoid tumors [Table 4].

Other trials with pazopanib, and with other multitarget agents such as famitinib (c-kit, platelet-derived growth factor receptor (PDGFR), VEGFR2, VEGFR3, Flt1 and Flt3 inhibitor), regorafenib (c-Raf; BRAF, VEGFR-1,2,3; PDGFRα, Fibroblast Growth Factor Receptor (FGFR)-1; c-kit; RET; Flt-3 inhibitor), and nintedanib (VEGFR, FGFR, PDGFR inhibitor) are ongoing. Some of them are also enrolling patients with bronchopulmonary NETs (Clinical Trial: NCT01280201; NCT01994213; NCT02259725; NCT02399215).[126-128]

EGF AND ITS RECEPTOR AND TGFα

EGFR/AKT/mTOR pathway activation could be shown in all entities of NETs and was observed especially in tumors with high grading and poor prognosis. Typical and atypical bronchopulmonary carcinoids[129] and gastrointestinal-neuroendocrine tumours (GI-NETs) and P-NETs present and over-regulate EGFRs.[130] [Figure 1] Papouchado *et al*.[131] in particular, described a higher presence of EGFR (> 91%) in GI-NETs, especially rectal NETs, than in P-NETs (< 25%).

An elevated presence of EGFR and transforming growth factor alpha (TGFα) in P-NETs was observed by Srivastava *et al*.[132] An elevated amount of secreted TGFα was detected in cultures of carcinoid tumors and pheochromocytomas, and the administration octreotide and anti-EGFR monoclonal antibodies seemed to reduce the secretion and the proliferative effect of TGFα.[133] Krishnamurthy *et al*.[134] showed a high expression of TGFα in GI NETs (72%) without any correlation with tumor size, grading, and other pathologic features, but only depending on the technique used (immunohistochemistry or northern blot analysis).[133] In rectal NENs TGF-α expression seemed to be increased in lesions larger than 5 mm and tumors with higher Ki67 index.[135] Despite the heterogeneity of these results, EGFR and its signal transduction pathways (RAS-RAF-MAPK) might represent an interesting target for the treatment of NETs.

In fact, a synergistic effect in determining apoptosis in atypical carcinoid cell lines was demonstrated by the association of epidermal growth factor (EGF) receptor inhibitors (erlotinib) with everolimus in *in-vitro* studies.[129]

A phase II trial evaluated gefitinib in 96 pretreated patients affected by GEP-NETs achieved prolonged disease control with rare objective responses; the study drug was well-tolerated.[136]

OTHER TYROSINE KINASE INHIBITORS AND IMMUNOTHERAPY

Beta fibroblast growth factor (bFGF) and c-kit/Platelet Derived Growth Factor (PDGF) inhibitors are being developed, based upon the variable expression of bFGF, c-kit and PDGF in NETs.[137-139]

Despite little systematic and rigorous in-depth analysis of immunotherapy in NETs (interferon and dendritic cell vaccines), the recent progress in targeting of Cytotoxic T lymphocyte antigen-4 and PD-1 provide opportunities for future advances.[140] Further studies are necessary to examine the variable expression of PD-1, PD-L1/L2 in NENs.

CONCLUSION

The predictive and prognostic characteristics of NETs are still under investigation to individuate a pattern of peculiar molecular genetic alterations in each kind of neoplasm. The aim is to find a correlation of specific abnormalities implicated in carcinogenesis and dissemination that may provide potential targets for tailored biotherapy.

In GEP and lung NETs, carcinogenesis and dissemination often involves SSTRs, mTOR/Akt/PI3K and PTEN, IGF-1, VEGF, EGF, TGF, FGF and c-kit/PDGF and its corresponding receptors, markers whose established value may more thoroughly define an appropriate course of treatment.

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