The mTOR signalling pathways in the pathogenesis and treatment of neuroendocrine tumours

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ABSTRACT

Neuroendocrine tumours (NET) are a rare and heterogeneous group of neoplasms.

The majority of patients are diagnosed with locally advanced or metastatic disease, and curative surgery is rarely an option. Treatment approaches involving targeted therapy, including the use of agents inhibiting the mTOR signalling pathways involved in neuroendocrine tumourigenesis, provide new therapeutic options for patients with NETs.

KEY WORDS: neuroendocrine tumours (NETs), mTOR signalling pathway, mTOR inhibitors

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INTRODUCTION

Neuroendocrine tumours (NET) are a heterogeneous group of rare neoplasms. Most of them are non-functioning, which is why they are diagnosed at an advanced stage only, making radical surgical treatment impossible. The course of the disease varies too, ranging from relatively mild local lesions to aggressive and quickly metastasising ones. Hence, patient prognosis may be very different, with 5-year survival ranging from 15% to 95%, depending on the case in question [1, 2].

Biological properties of neuroendocrine tumours, related to the expression of many growth factors and their receptors, including VEGF (vascular endothelial growth factor), PDGF (platelet derived growth factor) and their receptors, bFGF (basic fibroblast growth factor), IGF1 and its receptor (IGF1R, insulin-like growth factor receptor), EGF (epidermal growth factor) and its receptor EGFR (epidermal growth factor receptor), c-MET (hepatocyte growth factor receptor) and somatostatin receptors, and the fact that the tumours are highly vascularized extend the possibilities of treatment involving biologics or molecular targeted agents [4].

mTOR signalling pathways

mTOR (mammalian target of rapamycin) is presently considered to be a new and important target in the treatment of neuroendocrine tumours. mTOR is an intracellular serine/threonine protein kinase, acting as the main regulator of cell proliferation, angiogenesis and metabolism. It is a key intracellular meeting point of many signalling pathways which are abnormally activated in neoplasms [5].

The PI3K/AKT/mTOR SIGNALLING PATHWAY

The PI3K (phosphatidylinositol 3-kinase)/AKT/mTOR signalling cascade is one of the chief signalling pathways related to the activity of receptor tyrosine kinases (RTKs) in cancer cells [6]. RTK activation leads to autophosphorylation of the cytoplasmic domain, which subsequently interacts with the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K). The subunit may also be indirectly activated by contact with insulin receptor substrates (IRS-1/2) [7]. As a result of p85 activation, the p110 catalytic subunit of PI3K is stimulated. The p110 subunit mediates conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3). Additionally, PI3K may undergo activation via direct contact of RAS with the p110 subunit [6]. PI3K activity is inhibited by PTEN (phosphatase and tensin homolog), responsible for PIP3 dephosphorylation. PIP3 activates the AKT serine/threonine kinase on the internal surface of cell membrane, followed by AKT phosphorylation of a series of proteins involved in proliferation and apoptosis control within the cytoplasm and the nucleus [8].

One of the key elements activated by AKT is the mTOR serine/threonine kinase. The TOR protein family performs different functions and participates in the regulation of many cellular processes and protein translations. It is involved in the organization of the actin cytoskeleton, relocation of intracytoplasmic structures, degradation of proteins, signalling cascade of the C protein kinase, and in the ribosomal biogenesis [9, 10]. The mTOR protein regulates important signalling pathways that activate cellular proliferation, modulating and transmitting signals from the membrane receptors [11]. The mTOR protein is to be found in two structurally distinct complexes: mTORC1 and mTORC2. Both of the complexes additionally contain the GbL protein (G protein β-subunit-like protein), and the raptor (regulatory-associated protein of mTOR in mTORC1) or rictor (rapamycin-insensitive companion of mTOR in mTORC2) proteins [11–15]. The mTORC1 complex phosphorylates effector proteins, the S6 kinase 1 (S6K1, p70S6K) and the 4EBP1 protein binding the early eukaryotic initiation factor 4E (eIF4E), which control the translation of particular genes [12]. On the other hand, mTORC2 controls the actin cytoskeleton, and regulates the activity of AKT/PKB [16, 17]. Phosphorylated AKT may activate mTORC1 via 2 pathways involving the TSC1/TSC2 complex or the PRAS40 protein [18]. In a cell which contains an adequate amount of nutrients, AKT inactivates the TSC1/TSC2 tumour suppressor complex [19]. The inactivated TSC1/TSC2 complex ceases to inhibit the activity of the GTP-binding protein, which can directly activate the mTORC1 complex. Phosphorylation of the PRAS40 protein by AKT switches off its inhibitory impact on mTORC1 [18]. It appears that the less known mTORC2 complex also plays an important part in neoplastic cells. mTORC2 acts as the phosphoinositide-dependent kinase-2 (PDK2), causing AKT phosphorylation. As a result, the FOXO proteins, performing the function of a transcription factor and apoptosis activator, undergo phosphorylation and inactivation [20]. Moreover, TORC2 is also responsible for the transcription of two hypoxia-inducible factors, HIF-1a and HIF-2a [21], which determine the malignant phenotype of neoplastic cells, and are responsible for resistance to chemotherapy.

INVOLVEMENT OF THE MTOR PATHWAY IN THE PATHOGENESIS OF NEUROENDOCRINE TUMOURS

Results of whole-exome sequencing of sporadic pancreatic NETs indicate that alterations in the pathways genes MEN-1, DAXX/ATRX and mTOR (including the PTEN and TCS2 genes) are frequently observed in neuroendocrine tumours [22]. Based on gene expression profiling, the role of PI3K/AKT/mTOR in the development of sporadic pancreatic NETs has been confirmed [23–25]. Analysis of the molecular mechanisms behind neuroendocrine tumours has demonstrated that predisposition to NET is related to the damage of the PTEN suppressor gene, and consequently to the lack of activity of the PTEN phosphatase [24, 25]. Additionally, genome sequence analysis of sporadic pancreatic NETs has demonstrated somatic mutations in around 15% of the mTOR pathway-related genes: PTEN, TSC2 and PIK-3CA [22, 23]. The PTEN gene mutations are rare and account for only around 7–9% of the cases [25–27]. Additionally, in one third of the sporadic pancreatic NETs, deletion of 10q (PTEN) as well as deletion of 16p (TSC2) has been reported [28, 29]. Reduced expression of TSC2 as well as PTEN, a gene regulating the mTOR activity via the PI3K/AKT pathway, has been observed in 75% of the pancreatic NET patients [23]. Low PTEN expression appears to be associated with a shorter time to disease progression, and shorter median survival [23]. Recent findings point to the different expression of mTOR and mTOR-related proteins depending on the tumour primary location. The expression is higher in foregut tumours as compared to the midgut ones [30]. It has also been shown that in the case of midgut NET tumours, the TSC1 and TSC2 expression is normal, unlike in the pancreatic NETs, where low expression of PTEN, TSC1 and TSC2 is reported [25]. The results indicate different mechanisms behind the mTOR pathway activation in neuroendocrine tumours of different primary foci [31].

Most NETs are sporadic, but there is a small group of neuroendocrine tumours which form part of familial genetic syndromes. A small group of patients (< 5%) suffering from neurofibromatosis type 1 (NF1) develop catecholamine-producing tumours or neuroendocrine tumours involving the duodenal papilla. The NF1 gene encodes the neurofibromin protein, which inhibits the PI3K/AKT/mTOR pathway via RAS suppression. In patients with tuberous sclerosis (TS), tumours are related to the inactivity of the TSC1 and TSC2 suppressor genes, and they are also regulated by neurofibromin thanks to the mTOR pathway activation [32].

mTOR INHIBITORS IN CLINICAL PRACTICE

Rapamycin (sirolimus), a macrolide antibiotic, and its derivatives (temsirolimus and everolimus) are inhibitors of the mTOR serine/threonine kinase. The compounds have antiproliferative and antiangiogenic properties. They inhibit the growth and proliferation of tumour cells, endothelial cells, fibroblasts, and vascular smooth muscle cells [33]. It is assumed that rapamycin has a two-stage mechanism of action, with the complex of rapamycin-acceptor protein FKBP12 created at the first stage, and mTOR activity inhibited by the newly created complex at the second stage. As a result, the activity of mTOR effector proteins (p70S6K and 4E-BP1) is inhibited, cells accumulate in the G1 phase of the cell cycle, and apoptosis is induced [34].

So far, only one drug from the group, everolimus, has been applied in clinical practice to treat neuroendocrine tumours.

The first phase II clinical trial which demonstrated therapeutic activity of everolimus included 30 subjects with pancreatic NET. They received combined treatment with a long-acting somatostatin receptor analogue (Octreotide-LAR) dosed at 30 mg every 4 weeks, and with the study drug, everolimus, dosed at 5 mg and 10 mg. Therapeutic response, based on the RECIST criteria, was reported in 27% of the subjects, and progression-free survival (PFS) was 50 weeks in the group dosed at 10 mg [35, 36].

Another phase II trial confirmed the efficacy of everolimus in the treatment of advanced pancreatic neuroendocrine tumours. The RADIANT-1 study assessed the efficacy of everolimus monotherapy and everolimus in combination with octreotide LAR in patients with advanced and chemoresistant pancreatic NETs. The patients were divided into two arms, one treated with everolimus dosed at 10 mg daily (115 subjects), and the other (45 subjects) with octreotide-LAR combined with everolimus dosed at 10 mg. Complete response and disease stabilization, based on the RECIST criteria, was observed in 84% of the subjects from the combined therapy arm, and in 77% of the patients on everolimus solely. Similarly, median PFS was longer for the combined treatment arm, with 16.7 vs. 9.7 months, respectively. Tumour mass reduction by over 50% was reported in 56% and 49% of the subjects, respectively. Additionally, there was a correlation between the reduced concentration of chromogranin A and median PFS. The treatment was well-tolerated by the patients involved. There were very few grade 3 and 4 adverse events, including oral mucositis, fatigue, and diarrhoea [35].

Results of the phase III RADIANT-3 study, published in 2011, confirmed the efficacy of everolimus in the treatment of patients with well-differentiated advanced pancreatic neuroendocrine tumours. The study involved 410 subjects with advanced pancreatic NETs with radiologic progression within the previous 12 months. The patients were randomly assigned to receive everolimus dosed at 10 mg daily (207 subjects) or placebo in addition to best supportive care (203 subjects). The trial demonstrated a statistically significant improvement in PFS (primary endpoint), which amounted to 11 months in the everolimus arm vs. 4.6 months in the placebo arm. At 5%, complete response rate was low. The treatment was well-tolerated by the patients, and the most common adverse events included stomatitis (64%), rash (49%) and diarrhoea (34%). The most frequently observed grade 3 and 4 adverse events were stomatitis (7%), anaemia (6%) and hyperglycaemia (5%) [37]. During the 2014 ESMO Congress in Madrid, results pertaining to the secondary endpoint were presented, i.e. overall survival of the patients involved in the RADIANT-3 study. Median OS was 44.02 months (95% CI: 35.61–51.75) in the everolimus arm, and 37.68 months (95% CI: 29.14–45.77) in the placebo arm. The 6.34 months difference between the two arms was not statistically significant (HR = 0,94; 95% CI: 0.73–1.20; p = 0.3), but it resulted from the fact that once the main phase of the study has been completed, and after unblinding, the patients from the placebo arm were offered to cross over to everolimus. In the open-label phase of the study, patients continued treatment with everolimus until disease progression documented by the investigator. In the course of the study, 85% of the patients originally assigned to the placebo arm were eventually treated with everolimus. Thus, improvement in terms of OS is in line with the statistically significant improvement in PFS by 6.44 months, demonstrated during the primary analysis (HR = 0.35; 95% CI: 0.27–0.45; p < 0.001) [38].
The use of mTOR tyrosine kinase inhibitors, including everolimus, has been explored not only with reference to pancreatic NET, but also in the context of neuroendocrine tumours found in other parts of the body.

30 patients with midgut neuroendocrine tumours received everolimus with octreotide in a phase II trial. Partial response to treatment was reported in 17% of them, with median PFS of 63 weeks [35].

The randomized phase III RADIANT-2 study involved 429 patients with well-differentiated (77–82%) and moderately differentiated (30–38%) inoperable locally advanced or metastatic neuroendocrine tumours (primary focus: small intestine 51–53%, lung 5–15%, large intestine 14%, pancreas 11–15%, liver 7–11%, different location 40–48%) with symptoms of carcinoid syndrome. One arm of the study received everolimus combined with long-acting octreotide, and the other was put on octreotide plus placebo. The study endpoint was progression-free survival (PFS). However, results of the study cannot be considered as valid, as the data monitoring committee identified some discrepancies between the local analysis carried out in the different centres participating in the study, and the analysis conducted centrally. A tendency to improved PFS was noted, but the results were not statistically significant. Median PFS in patients treated with octreotide and everolimus was longer at 16.4 months as compared to 11.3 months in the control group (HR = 0.77; p = 0.026). Adverse events (mainly grade 1 and 2) were more frequently reported for the octreotide plus everolimus arm, and they included gastritis (62% vs. 14%), rash (37% vs. 12%), fatigue (31% vs. 23%) and diarrhoea (27% vs. 16%) [39].

Analysis of a subgroup of RADIANT-2 patients with advanced neuroendocrine lung cancer indicated that adding everolimus to octreotide LAR leads to a statistically non-significant improvement in median PFS compared to placebo plus octreotide LAR, with central radiologic assessment of HR = 0.72 (95% CI: 0.31–1.68; p = 0.228), and local investigator assessment of HR = 0.62 (95% CI: 0.29–1.31; p = 0.106) [40]. In another *post-hoc* analysis of a subgroup of RADIANT-2 patients with advanced colorectal NETs, whose treatment is most problematic nowadays, it was demonstrated that patients on everolimus with octreotide LAR had longer PFS (29.9 months; n = 19) than patients treated with placebo plus octreotide LAR (PFS 6.6 months; n = 20). Additionally, tumour mass reduction was observed more frequently in the mTOR inhibitor group than in the placebo arm, with 67% vs. 37%, respectively [41].

The most recent study, RADIANT-4, included 302 patients with neuroendocrine tumours of GI or lung origin (30% of the study subjects had lung lesions, and 24% of them had colorectal lesions) with confirmed progression. All patients were offered best supportive care, and they were randomized (2 : 1) to receive either everolimus or placebo. A statistically significant improvement in PFS was demonstrated, with median PFS (assessed centrally) of 11 months in the everolimus arm vs. 3.9 months in the placebo group (HR = 0.48; p < 0.00001). The overall survival (OS) data are not mature yet, but they show a tendency to reduced mortality risk by 37% thanks to everolimus. Another secondary endpoint of the study was the overall response rate (ORR), which amounted to 64% in the everolimus arm compared to 26% in the placebo arm. The adverse events reported in the study were similar to the ones documented in the previous studies. 63% of

the patients treated with everolimus suffered from stomatitis with ulceration, but it is worth noting that some of the earlier and present observations indicate that that particular adverse event is significantly associated with the drug's efficacy. The most common grade 3 and 4 adverse events associated with the treatment included stomatitis (9% of the everolimus patients vs. 0.5% of the patients on placebo), diarrhoea (7% vs. 2%, respectively) and infections (7% vs. 0%, respectively) [42]. According to the investigators, results of the RADIANT-4 clinical trial are consistent with the results of the previous studies, all pointing to the efficacy of everolimus in the treatment of neuroendocrine tumours, regardless of the primary lesion location.

During this year's GI-ASCO conference in 2016, results of another analysis of the RADIANT-4 study were presented, involving a subgroup of patients with neuroendocrine tumours of GI origin. Everolimus was shown to prolong progression-free survival by 6.8 months compared to placebo in patients suffering from advanced GI NETs. The above mentioned analysis included only those patients in whose case the primary tumour was located within the GI tract (n = 175) or the origin was not determined (n = 36). Median PFS was 13.1 months for the GI NET patients on everolimus as compared to 5.4 months in the same subgroup receiving placebo. Additionally, a 44% reduction in the risk of disease progression was reported for the patients receiving active treatment. The most common primary lesion location was the ileum (41% of the patients) and the rectum (23%).

Median PFS in patients with unknown disease origin was 13.6 months for the everolimus arm vs. 7.5 months for the placebo arm, with additional 40% reduction in the risk of disease progression reported in the everolimus-treated subgroup. The above presented study proves that the use of everolimus is beneficial, regardless of the previously administered therapy. All patients included in the trial had progressed following surgery (70% of the patients), chemotherapy (19%) or treatment with somatostatin analogues (59%).

SUMMARY

Basic research accomplishments, especially in the field of molecular biology, and the role of the mTOR signalling pathways, which appear to play an important part in the pathogenesis of neuroendocrine tumours, have made it possible to extend the therapeutic options addressed to patients with advanced NETs, by adding the new drug everolimus. New treatment algorithms are based on attempts to combine different molecular targeted drugs as well as to combine molecular targeted drugs with chemotherapy.

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