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New Drugs

Biologic rationale and clinical activity of mTOR inhibitors in gynecological cancer

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ABSTRACT

Advanced recurrent gynecological malignancies have a poor prognosis despite systemic treatment, which is usually cytotoxic chemotherapy. Responses are generally short-lived and more effective treatments are needed. Rationally designed molecularly targeted therapy is an emerging and important option in this setting. The mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase of the phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathway with a critical role in controlling cancer cellular growth, metabolism and cell cycle progression. Aberrant PI3K-dependent signaling occurs frequently in a wide range of tumor types, including ovarian, endometrial and cervical cancer. Early clinical studies of first-generation mTOR inhibitors have shown promising clinical activity in endometrial cancer. However, the molecular basis of sensitivity and resistance to these agents remains largely unknown. In this review, we will update the clinical and biological data underlying the development of first generation mTOR inhibitors in the treatment of gynecological tumors. The role of potential new combination regimens with mTOR inhibitors in gynecological cancers will also be discussed.

Introduction

Platinum-based chemotherapies remain the cornerstone in the treatment of advanced gynecological cancers. Although responses to first-line treatment are frequently observed, relapses are common and effective therapeutic options for recurrent disease are lacking.[1] Targeted agents are actively being evaluated in gynecological tumors.[2–4] mTOR is a serine-threonine kinase that regulates both cell growth and cell cycle progression through its ability to integrate signals from nutrient and growth factor stimuli.[5] Aberrant activation of the mTOR pathway may occur through increased signaling via growth factor receptors (e.g. insulin-like growth factor receptor, IGFR; epidermal growth factor receptor, EGFR), activating mutations or amplification of different pathway kinase genes,[6–8] or by loss of function of the phosphate and tensin homolog (PTEN).[9,10] These phenomena have been observed in a variety of tumors, including endometrial and ovarian cancers.[11,12] An interaction between certain human papilloma virus (HPV) oncoproteins and the mTOR pathway has also been reported, leading to explore the therapeutic potential of mTOR inhibitors in HPV-induced cervical carcinoma.[13,14]

Sirolimus (rapamycin [Rapamune]; Wyeth, Madison, NJ) and its derivatives (i.e. temsirolimus, everolimus, and ridaforolimus; also known as rapalogs) are immunosuppressor macrolides that block mTOR and yield antiproliferative activity in a variety of malignancies.[15,16] Sirolimus is used for prevention of organ rejection after solid organ transplantation.[17] Despite a robust rationale, sirolimus as a single agent has scarcely been evaluated in cancer patients. However, the combination of sirolimus and other targeted agents is generally well tolerated, and signs of antitumor activity have also been reported.[18,19]

Based on the results of large phase III randomized clinical trials, temsirolimus (Torisel; Pzifer, Philadelphia, PA, USA) and everolimus (Afinitor; Novartis Pharmaceuticals, Basel, Switzerland) were approved for the treatment of advanced renal cell carcinoma.[20,21] Temsirolimus has also been approved for the treatment of mantle-cell lymphoma,[22] and everolimus is now indicated in the treatment of advanced pancreatic neuroendocrine tumors.[23] Preliminary results from a randomized placebo-control phase III trial have recently shown that oral ridaforolimus (AP23573, MK-8669, formerly deforolimus; ARIAD, Cambridge, MA, USA), given

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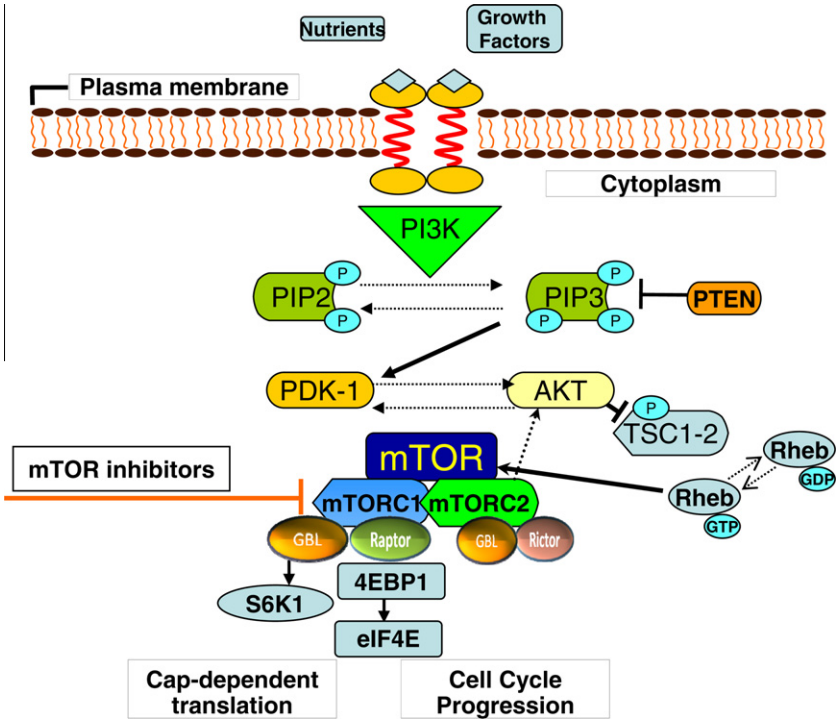

Fig. 1. mTOR/PI3K/Akt signaling pathway.

as maintenance therapy in patients with metastatic sarcoma significantly improves progression-free survival (PFS) in those patients who achieved stable disease (SD) or a better response after chemotherapy.[24]

This review will focus on the potential therapeutic role of the first generation mTOR inhibitors and discuss recent results of clinical trials of mTOR inhibitors in ovarian, endometrial and cervical cancer, as well as ongoing clinical studies. We will integrate the analysis of this clinical data with a comprehensive update of the biological rationale regarding mTOR inhibition in gynecological cancers and the future development of these combinations.

Molecular biology of the mTOR pathway

mTOR is a member of the PI3K-related protein kinase family. Growth factor receptor stimulation leads to activation of PI3K, which phosphorylates phosphatidylinositol-4,5-bis-phosphate (PIP2) to generate phosphatidylinositol-3,4,5-triphosphate (PIP3). The accumulation of PIP3 activates a signaling cascade starting with the phosphorylation (activation) of the protein serine–threonine kinase AKT by PDK1 (Fig. 1). The phosphatase and tensin homolog PTEN protein can dephosphorylate PIP3, reversing the action of PI3K, thereby modulating phosphorylated AKT (pAKT). AKT phosphorylates and inhibits the tuberous sclerosis complex (TSC), removing its inhibitory effect on Ras-related small GTPase Rheb (Ras-homolog-enriched-in-brain), which acts as a positive upstream regulator of mTOR. Activation of mTOR in complex with other proteins, in particular with the mTOR complex 1 (mTORC1), associated with the regulatory associated protein of mTOR (raptor), leads to phosphorylation of eukaryotic translation initiation factor 4E binding protein (4E-BP1) and ribosomal protein S6 kinase 1 (S6K1) (Fig. 1). In cancer cells, 4E-BP1 phosphorylation results in the initiation of translation. The activation of mTORC1 downstream targets leads to protein synthesis, such as cell cycle regulating proteins, vascular endothelial growth factor (VEGF), or c-Myc. Rapalogs bind intracellularly to the immunophilin FKBP-12 (FK 506 binding protein) creating a complex that inhibits the protein kinase activity of mTORC1.[25] mTOR complex 2 (mTORC2) couples with the rapamycin-insensitive companion of mTOR (rictor), and is functionally distinct from mTORC1. The mechanisms regulating mTORC2 complex are still not fully elucidated. Its activation promotes cell survival and actin cytoskeleton organization.[26] Rapamycin and rapalogs are primarily inhibitors of mTORC1, preventing phosphorylation of 4E-BP1, S6K1, and other proteins involved in cell cycle control, leading to growth arrest in the G_1 phase of the cell cycle, and reduced angiogenesis.[27] Interestingly, rapamycin can activate mTORC2 and consequently AKT at Ser473, which in turn may represent a potential mechanism of resistance.[26]

Resistance to rapalogs has also been related with the activation of different signaling cascades other than the PI3K/AKT/mTOR pathway. The inhibition of S6K1 by rapalogues can activate insulin receptor substrate 1 (IRS1), leading to a feedback loop mechanism that may reactivate AKT,[28] and preclinical evidence has shown that simultaneous targeting of IGFR and mTOR signaling pathways yields higher antitumor activity.[29] mTORC1 inhibition also results in a hyperactivation of the PI3K pathway and simultaneously an increase in signaling through the mitogen-activated protein kinase (MAPK) pathway.[30] Some studies have shown that aberrations in these two pathways may actually coexist in solid tumors.[31,32] On the one hand, it has been shown that the activation of the PI3K pathway may influence the sensitivity of *RAS* mutated cells to MEK inhibitors.[33] On the other hand, Wee et al. demonstrated that *PTEN* mutations also confer resistance to MEK inhibition.[32] These findings provide a strong rationale for further clinical evaluation of combinatorial strategies with MAP/ERK (MEK) and mTOR/PI3K/AKT inhibitors.

Sensitivity to mTOR inhibitors is thought to be related to the deregulation of critical elements of the pathway. Results from preclinical models suggest that genetic alterations and aberrant protein expression resulting in pathway activation may correlate with the clinical activity of mTOR inhibitors.[34] Conceivably, tumors