Biologic Therapies and Personalized Medicine in Gynecologic Malignancies

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KEYWORDS

• Biologic therapies • Personalized medicine • Malignancies • Gynecology

KEY POINTS

- Personalized medicine has been championed as the next frontier in solid tumor treatment development.
- Through advances in human genomic sequencing, multiple cellular and molecular pathways have been identified to potentially serve as targets for drug development for gynecologic malignancies on an individualized basis.
- Currently, treatment studies have focused on stromal, vascular and cell signaling targets.
- Although results to date for biologic therapies have been mixed, great promise remains.

The concept of personalized medicine has been championed as the next frontier in solid tumor treatment development. The goal is to identify and then target a specific protein or pathway that is upregulated or overexpressed in tumors. Traditionally, treatment of gynecologic tumors has relied on the combination of surgical cytoreduction and cytotoxic chemotherapy to improve outcomes for patients with pelvic malignancies. Unlike many other oncologic subspecialties, however, rates of relapse and overall survival (OS) have improved only modestly over the past couple of decades despite the continued pursuit for novel chemotherapeutic regimens. As such, research in the field of female cancers has more recently focused on the highly

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variable molecular-based causes of oncologic transformation and cell growth. Through advances in human genomic sequencing, multiple cellular and molecular pathways have been identified to potentially serve as targets for drug development on an individualized basis. A better understanding of the biology of gynecologic malignancies has also led to a greater appreciation of the interconnectedness of the numerous cell signaling pathways that work together to produce states of heath and disease.

Not surprisingly, myriad treatment possibilities have encompassed stromal, vasculature, and cell signaling targets. Early success with antiangiogenic agents has become well-known in the field of ovarian cancer, but many other lesser known agents are being investigated in preclinical and early phase trials for not only ovarian but also cervical and uterine cancers. Results to date for biologic therapy development have been mixed, yet great promise remains. In this review the authors focus on the main categories of molecular targeting for ovarian, uterine, and cervical cancers and highlight key recently completed and current clinical trials.

CELL SIGNALING PATHWAYS

One of the most exciting new areas of research and drug development is in the area of cell signaling pathways. Although it is well-known that the initial insult of many malignancies results from numerous genetic and epigenetic circumstances, it is the maintenance of such neoplastic conditions that has prompted researchers to focus on the numerous cell signaling pathways that exist to maintain and perpetuate the survival of a malignant phenotype.[1] One such pathway that has been targeted as an important player in numerous solid organ malignancies is that of the phosphatidylinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) cell signaling pathway.[2-6] This pathway has been noted in recent years to be a key regulator of cell cycle initiation and survival, as well as protein synthesis and glucose metabolism.[1]

AKT is often seen as the central agent in the pathway, with multiple downstream pathways and feedback loops that make it an integral part of normal cell growth and proliferation.[2-6] Upstream from the AKT complex lies P13K, an active kinase that is encoded by PIK3CA that in turn activates AKT in the signaling cascade, thereby mediating survival signals that protect cells from apoptosis. Not surprisingly, many studies have demonstrated high rates of AKT hyperactivation in various cancers including ovarian malignancies. Yuan and colleagues[4] demonstrated AKT activation in 36% of ovarian cancer specimens assessed for AKT and PI3K activity. The majority of these cancers were histologically high grade and late stage tumors. In nearly half of these cases, high levels of PI3K were also noted, with the majority also exhibiting AKT amplification. Similarly, other amplifications and mutations have been observed in PIK3CA, with rates as high as 15% in various cancers.[1] Various aberrations have been found in uterine, cervical, and ovarian cancers, with particular overrepresentation in endometrioid and clear cell histologies.[7]

Another key player in the PI3K/AKT/mTOR pathway is PTEN that serves to inhibit PI3K signaling through dephosphorylation of the second messenger PIP3.[3,5,6] Inhibition of PI3K thus results in a breakdown of the normal apoptotic mechanisms necessary for preventing neoplastic proliferation. The second most commonly mutated tumor suppressor gene after p53, PTEN is often inactivated through various mechanisms in a number of malignancies including endometrial cancers.[2] More specifically, inactivation of P13K signaling through either PIK3CA or PTEN mutations is seen in approximately 40% of endometrial cancers in comparison with less than 5% of ovarian malignancies.[8]

A number of drugs targeting the PI3K/AKT/mTOR pathway have begun to emerge. Inhibitors of P13K are now ongoing in early clinical development, whereas AKT and