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A REVIEW ON PI3K INHIBITORS IN OVARIAN CANCER

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ABSTRACT

Ovarian cancer remains a major cause of gynaecologic cancer death, and the PI3K/AKT/mTOR pathway is often aberrant in its development. This review exhaustively reviews the therapeutic utility of PI3K inhibitors in ovarian cancer as pan-PI3K, isoform-selective, and dual PI3K/mTOR inhibitors. Despite their promising preclinical and clinical activity, these drugs are not as effective as they are when used alone due to limitations such as drug resistance, toxicity, and activation of compensatory pathways. To overcome these limitations, recent research has suggested that combining therapies that include PARP inhibitors, MEK/ERK inhibitors, chemotherapy, immune checkpoint inhibitors, and anti-angiogenic agents is necessary. The review focuses on the current evidence on PI3K-targeted therapies, their resistance mechanisms, and new combination regimens to date. It emphasizes the necessity of further clinical study to establish their place in improving the survival of ovarian cancer patients.

KEYWORDS: PI3K inhibitors, ovarian cancer, targeted therapy, combination treatment, drug resistance, PI3K/AKT/mTOR pathway.

INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer-related deaths in women and is the second most common gynaecologic malignancy in the United States. An estimated 207,252 people died and about 313,959 new cases were diagnosed worldwide in 2020.[1] It is a malignant tumour that develops in the ovaries and has the potential to affect nearby structures like the fallopian tubes or peritoneum (the inner lining of the abdomen). Risk factors include genetic susceptibility, obesity, hormone therapy following menopause, fertility medication, and nulliparity. Treatment for ovarian cancer typically involves a combination of surgical intervention and chemotherapy. Surgery aims to remove the tumour, often involving the uterus, ovaries, fallopian tubes, and omentum. Drugs like carboplatin and paclitaxel are commonly used in chemotherapy to target any remaining cancer cells. In advanced stages, debulking surgery is performed to minimize tumour burden prior to chemotherapy. Newer approaches, such as targeted therapies and immunotherapies, are also being explored to enhance outcomes.[1]

Phosphatidylinositol 3-kinases (PI3Ks) are a family of enzymes involved in various cellular functions such as growth, proliferation, differentiation, motility, survival, and intracellular trafficking, which are frequently dysregulated in cancer.[2] PI3Ks are divided into Class I, II, and III, with Class I being the main contributor to cancer-related signalling pathways. It is a heterodimer comprised of a catalytic subunit (p110) and a regulatory subunit (p85). The p110 catalytic subunit includes four isoforms p110 α, p110 β, p110 δ, and p110 γ, which are encoded by PIK3CA, PIK3CB, PIK3CD, and PIK3CG genes, respectively. Class I PI3Ks are further divided into class IA PI3K (p110 α, p110 β, p110 δ) and class IB PI3K (p110 γ) depending on the type of regulatory subunits (p85 for classes IA, p84/p101 for classes IB).[3]

PI3Kα (p110α) receptors are present everywhere in the body, but especially high in epithelial cells of the breast, prostrate, lung, colon and in endothelial cells. It is also present in liver, muscle and fat cells which are involved in insulin signalling.[34] They are mainly involved in cell growth, metabolism and cancer progression.[35] PI3Kβ (p110β) receptors are widely expressed, but higher in platelets involved in blood clotting.[36] it is also seen in neurons, prostrate and ovarian cells.[37] They are mainly involved in thrombosis, cell migration and in certain type of cancers.PI3Kγ (p110γ) receptors are primarily located in immune cells and cardiovascular tissues.[38] They are mainly involved in inflammation, autoimmune disease and heart contractility. PI3Kδ (p110δ) receptors are mostly seen in hematopoietic (blood) cells.[40]

It has also seen in B cells, T cells and mast cells.[41] They are mainly involved in immune responses and B cell malignancies.[42]

PI3K/AKT/mTOR pathway is the most frequently altered pathway in most cancers. Studies have shown that ovarian cancer often involves alterations in components of the PI3K/AKT/mTOR pathway, including mutations in the PIK3CA gene, which encodes the catalytic subunit of Class I PI3K, as well as mutations in mTOR, AKT1, and AKT2 genes.[4]

In a study involving mouse models, it is evident that inhibition of PI3K/AKT/mTOR was found to delay tumour growth, which is a practical proof of the incorporation of PI3K/AKT/mTOR pathway inhibitors as newer therapeutic strategies in ovarian cancer.[7]

PI3K/AKT/mTOR pathway and its dysregulation in ovarian cancer

PI3K/AKT/mTOR pathway is activated by extracellular signals such as growth factor, insulin or cytokines and which binds to receptor tyrosine kinase receptors. The ligand binding leads to the autophosphorylation of the receptor, which acts as the docking site for the PI3K enzyme. PI3K is a heterodimer which consists of a regulatory subunit (p85) and a catalytic subunit (p110). The regulatory subunit binds to the phosphorylated receptor tyrosine kinases which in turn activates the catalytic subunit. Activated PI3K phosphorylates membrane phosphatidyl insitol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 acts as a second messenger which recruits AKT (protein kinase B) via its pleckstrin homology (PH) domain to the cell membrane. Then AKT is activated and phosphorylates numerous downstream targets which leads to diverse cellular responses like cell survival, cell growth, cell proliferation and metabolism. AKT also activates mTOR signalling pathway.[4]

PI3K/AKT/mTOR pathway is dysregulated mostly in ovarian cancer. The study by Huang et al using array comparative genomic hybridization (aCGH) reveals that this pathway is frequently altered in ovarian cancer.[5] The increased number of copies of genes PIK3CA (encodes the p110α catalytic subunit of PI3K), PIK3CB (encodes the p110β catalytic subunit), and PIK3R4 (encodes a regulatory subunit of PI3K) indicates increased activity of PI3K, which leads to ovarian cancer.[5] The PI3KR1gene, which encodes for p85 regulatory subunit was found to be mutated in 3.8 percent of ovarian cancer patients.[6] Other mechanisms involved in the hyperactivation of this pathway include; mutations in AKT

isoforms, loss of negative regulator PTEN.[4] As a result of all these, there is an increase in cell growth and proliferation which leads to cancer.

Inhibitors of PI3K/AKT/mTOR signalling pathway

Inhibitors of the PI3K/AKT/mTOR signalling pathway are classified into four major categories, i.e. mTOR inhibitors, PI3K inhibitors, dual mTOR/PI3K inhibitors and AKT inhibitors. Mabuchi et al studied the role of PI3K-Akt-BAD cascade in paclitaxel-resistant SW626 human ovarian cancer cell line and found that it has a major role in ovarian cancer.[8]

Pan-PI3K inhibitors

Pan-PI3K inhibitors target all isoforms of class 1 PI3K involving α, β, γ, δ. They have a broader mode of action and are used in cancer involving all isoforms.[9] **Buparlisib** (BKM120) is the first and potent Pan-PI3K inhibitor which is extensively evaluated in major type of cancer including ovarian cancer.[10] Buparlisib has been proven to have an effect on the cell cycle and apoptosis in lung cancer, breast cancer, ovarian cancer, and many other types of cancer.[11]

The first in human phase 1 clinical trial evaluated in **pictilisib** (GDC- 0941), which is a potent pan-PI3K inhibitor, in 60 patients with advanced solid tumours.[12] The results show promising signs of tumour responses in many cancers including ovarian cancer. Some common side effects like mild nausea, fatigue, and rash are observed.

Patnaik *et al* conducted a human phase 1 study of **copanlisib**, which is an intravenous pan-PI3K inhibitor.[13] It is evaluated in 60 patients with advanced solid tumours including ovarian cancer, assessing the safety, efficacy and pharmacokinetics. Plasma copanlisib level shows dose-dependent pharmacokinetics, achieving therapeutic considerations. Biomarker analysis included PI3KCA, KRAS, BRAF, with PTEN loss and PIK3CA mutations leading to better responses. A significant reduction in 18FDG uptake was observed in patients when performing (18F)-fluorodeoxyglucose positron emission tomography (18FDG-PET).[13] All these support copanlisib role in targeting PI3K pathway dysregulation in cancer.

PX-866 shows significant *in vivo* antitumour activity against OvCar-3 human ovarian cancer xenografts in immunodeficient mice.[14] it also synergized with radiation, highlighting its potential as a combination therapy in ovarian cancer.

Isoform specific PI3K inhibitors

These inhibitors selectively target isoforms of PI3K, allowing more precise targeting of pathways involved in cancer. PI3K α inhibitors target PI3K/AKT/mTOR pathway which is involved in cell survival, growth and proliferation. PI3K α inhibitor causes arrest of G1 phase of cell cycle without killing.[17]

Alpelisib, an oral PI3K alpha selective inhibitor had shown promising activity in ovarian cancer.[15] A study conducted involving 36 patients with PIK3CA-mutated advanced ovarian cancers received alpelisib 300 mg orally once daily. To assess the antitumor activity of alpelisib, the objective response (ORR) and disease control rates (DCR) are taken. The results showed that the ORR was 28% and the DCR was 61%, with the greatest benefit observed in patients with endometrial ovarian cancer.[15] **INK1117** is another reported PI3Kα inhibitor in phase I clinical trials for the treatment of solid tumours.[16] Preclinical studies reveal that **GSK2636771**, a selective p110β inhibitor can be active in PTEN-deficient and PIK3CB-aberrant advanced solid tumours.[18]

Resistance to PI3K inhibitors in ovarian cancer

Resistance to PI3K inhibitors in ovarian cancer arises through several key mechanisms:

- **Genetic Variations**

  Mutations in the PIK3CA gene, particularly exon 20 p.H1047R, increase AKT activity and are associated with a diminished response to treatment. Moreover, tumours with multiple or sub clonal PIK3CA mutations tend to exhibit less sensitivity to these inhibitors.[48]

- **PTEN Loss**

  While the absence of PTEN activates the PI3K pathway, it can also lead to resistance against PI3Kα-specific drugs like alpelisib, as PTEN-deficient tumors may rely more heavily on alternative PI3K isoforms such as PI3Kβ.[49]

- **Activation of Alternative Signalling Pathways**

  Cancer cells can compensate by activating other pathways, such as Ras/Raf/MEK/ERK and Wnt/β-catenin, which help them survive despite PI3K pathway inhibition.[50]

- **Secondary Genetic Changes and Feedback**
  Tumors may acquire additional mutations or activate feedback mechanisms that restore PI3K signalling, reducing the effectiveness of the inhibitors initially used.[49]

These diverse resistance pathways emphasize the challenge of targeting the PI3K pathway in ovarian cancer and suggest that combination treatment approaches might be necessary to improve outcomes.

Dual PI3K/mTOR inhibitors

Apitolisib showed antitumour activity in some tumours that are mediated by the PI3K–PTEN–AKT–mTOR pathway, including PIK3CA mutant ovarian cancer.[23] The limitation of apitolisib in ovarian cancer is its lack of tolerability as a single agent, with severe toxicities like pneumonitis at higher doses. While modest antitumor activity was noted, overall effectiveness was suboptimal, and combination regimens were required to enhance treatment. The complex biology of ovarian cancer with high levels of genomic aberrations can also influence the drug's effectiveness and complicate treatment responses. Thus, while apitolisib is promising, a more strategic approach must be employed to maximize its benefits in ovarian cancer patients.

Dual mTOR/PI3K inhibitors like **Gedatolisib** and PF-04691502 are pivotal in the treatment of ovarian cancer by inhibiting key signalling pathways that are frequently dysregulated in the disease. The study confirmed that the inhibitors exhibit pan-tumour activity against a broad spectrum of ovarian cancer xenograft models by causing tumour stasis and early volume reduction following treatment.[24] The activity was primarily based on increased apoptosis compared to decreased cell proliferation, indicating an unconventional mechanism of activity with potential in the treatment of ovarian cancer. Biomarkers like pS6 can be utilized to predict therapeutic response, giving way to intensified personalized therapy of ovarian cancer patients.[24]

Dactolisib has been very effective in the treatment of ovarian cancer, especially when combined with fatty acid synthase (FASN) inhibitors since the combination has the effect of increased inhibition of cancer cell growth.[25] The study indicates that use of dactolisib can inactivate the PI3K-mTORC1 pathway, but this can also result in compensatory activation of the MAPK pathway, which can reverse the effectiveness of treatment. However, the use of dactolisib and FASN inhibitors has been found to be more effective than the use of either

treatment alone. Therefore, dactolisib is a promising candidate for combination therapy in the treatment of ovarian cancer, especially in tumours with hyper-activated PI3K-mTORC1 signalling.[25]

Combination of PI3K inhibitors and PARP inhibitors

Wang et al conducted a study by exposing three wild types of PIK3CA ovarian cell lines to a PI3K inhibitor BKM120 and PARP inhibitor Olaparib.[19] The effect of BKM 120 alone or in combination with olaparib was evaluated by using cell count kit (CCK8) assay, immunoblotting, comet assay, flow cytometry and immunofluorescence assay. The results reveal the synergistic effect of these blocks the growth of three wild-type PIK3CA ovarian cancer cell lines and explants of primary ovarian tumour specimens.[19] BRCA downregulation is a predictive biomarker in this combination therapy.[20] Studies suggest that the combination of AKT inhibitor and PARP inhibitor is effective in recurrent ovarian cancer patients.[21]

The resistance to PARP inhibitors in ovarian cancer can be challenging. The mechanism by which resistance occurs includes resistance to homologous recombination repair, and those don't. Restoration occurs through re-expression of silenced gene or rewiring of the DNA damage response. Other mechanisms include increased PARPi reflux, altered PARP, dysregulation of replication fork reversal. combination therapy with PI3K inhibitors shows promising activity and overcoming the resistance.[22]

Olaparib and alpelisib are being explored for synergistic ability in the treatment of ovarian cancer, particularly in patients with epithelial ovarian cancer that is platinum-resistant and HRR-proficient.[26] The combination of the two agents is aimed at maximizing the therapeutic benefit over monotherapy. The combination in a phase 1 trial exhibited a response rate of 33% in BRCA wild-type, platinum-resistant ovarian carcinomas, which is significantly higher compared to the anticipated response rate from monotherapy with olaparib and alpelisib, at around 4-5% and less than 5%, respectively. The rationale for the combination regimen is founded on preclinical evidence showing that alpelisib, a PI3K inhibitor, has the ability to sensitize HRR-proficient tumors to olaparib, a PARP inhibitor, and enhance the outcome of treatment. The research also established that the combination was characterized by manageable toxicities without unexpected toxicities, indicating the combination is suitable for further clinical studies. In conclusion, the information supports the hypothesis that

alpelisib and olaparib combination would be a novel therapeutic regimen in treating patients with particular profiles of ovarian cancer, which necessitates further clinical studies.[26]

Combination of PI3K inhibitors and MEK/ERK inhibitors

In ovarian cancer, the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK kinase signalling pathways are frequently dysregulated and thus promising targets for therapy.[28] Research indicates that dual inhibition of PI3K/mTOR and ERK signalling pathways is effective in inhibiting cell proliferation and inducing cell death, even in drug-resistant cells.[29]

The researchers tried two cancer drugs specifically targeting PI3K and mTOR—PF-04691502, which targets both PI3K and mTOR, and PD-0325901, a MEK inhibitor—on a wide variety of ovarian cancer cell lines that cover all the major subtypes.[29] They quantified how well each drug inhibited cancer cell growth as well as examined the molecular signatures of these cells, such as global gene expression profiles, mutations in key PI3K/mTOR and RAS/ERK pathway genes, and baseline activity of these pathways.

A study investigates the therapeutic value of a dual PI3K/mTOR inhibitor, PF-04691502, in a Kras G12D mutation and Pten deletion-initiated ovarian cancer mouse model. PF-04691502 temporarily inhibited the growth of the tumour but did not lead to regression. To make it more potent, the researchers combined it with the MEK inhibitor to increase survival. The dual therapy bypassed resistance mechanisms that accompanied the activation of the RAS/MAPK pathway, demonstrating the importance of multi-pathway inhibition in cancer therapy.[27]

Combination of PI3K inhibitors and chemotherapy

Treatment of PI3K inhibitors with chemotherapy (e.g., platinum drugs, paclitaxel) in ovarian cancer is intended to overcome chemoresistance by inhibiting survival signalling and improving DNA damage. Preclinical data indicate that PI3K inhibitors (e.g., alpelisib, copanlisib) make tumours sensitive to chemotherapy, especially in PIK3CA-mutant or PTEN-deficient tumours. Initial clinical trials (e.g., buparlisib + carboplatin/paclitaxel) proved some efficacy but encountered dose-limiting toxicities (neuropathy, myelosuppression). Continued research aims to optimize combinations and biomarker-based patient selection to maximize results while keeping side effects under control.

The research investigated the combination of alpelisib, a PI3K selective inhibitor, with paclitaxel in treating advanced solid tumours, including ovarian cancer.[30] It was interested in understanding how the activation of the PI3K pathway causes resistance to paclitaxel and hypothesizing that the combination could enhance treatment response. A total of 19 patients were treated, and the trial indicated a difficult safety profile with great frequency of adverse effects such as diarrhoea and hyperglycaemia. The highest tolerated dose of alpelisib was 150 mg per day when combined with paclitaxel. Even though the safety issues were significant, the trial identified the possibility of inhibiting the PI3K pathway to increase sensitivity in chemotherapy-resistant ovarian cancer cells.

A study conducted by using the combination of buparlisib, a pan-PI3K inhibitor, with paclitaxel, a chemotherapeutic agent, as therapy for treating ovarian cancer.[31] There is preclinical evidence that the buparlisib-olaparib combination has synergistic activity, pointing to enhanced efficacy beyond BRCA-related or homologous recombination-deficient tumours. A particular clinical trial with the combination of buparlisib and paclitaxel has shown encouraging results, with good tolerance in patients, especially those with platinum-resistant disease. The results indicate that this combination approach may improve overall tumour response rates and could be used in a wider patient population than initially thought. Nevertheless, additional studies are required to confirm these findings and fine-tune treatment protocols.

Combination of PI3K inhibitors and immune check point inhibitors

The use of immune checkpoint inhibitors (ICIs) in combination with PI3K (phosphoinositide 3-kinase) pathway inhibitors is an attractive therapeutic approach in ovarian cancer.[32] The PI3K-AKT signalling pathway is frequently hyperactivated in ovarian cancer, promoting tumour growth and immunosuppression. Through inhibition of this pathway, it is possible that anti-tumour immunity can be augmented, especially when combined with ICIs against PD-1/PD-L1. Research suggests that PD-L1 can support the survival of cancer cells through the AKT-mTORC signalling pathway, and the combination of PI3K inhibitors and ICIs could reverse PD-L1's harmful effects and create a stronger immune response. Preclinical research proposes that the combination not only enhances the effectiveness of ICIs by inhibiting PD-L1 expression on tumour cells but also provides more favourable clinical outcomes in patients. Ongoing clinical trials are investigating the safety and efficacy of this combination

regimen, although challenges persist, such as balancing potential side effects and identifying optimal patient selection strategies based on biomarkers such as PD-L1 levels.

PI3K inhibitors + Anti-angiogenics (VEGF inhibitors)

Research investigates the interaction between the VEGF-A/VEGFR2 signalling pathway and the AKT/mTOR pathway in human epithelial ovarian cancer, with VEGF-A having a central role in such cancer.[33] The research presents that anti-VEGF-A therapies like bevacizumab have marked response and toxicity in ovarian cancer. There is an association between VEGFR2 activation and downstream AKT/mTOR signalling, specifically with phosphorylated VEGFR2 (pVEGFR2) and phosphorylated S6 (pS6), implicating VEGFR2's function in promoting tumour cell proliferation. Clinically, activated VEGFR2/AKT/mTOR signalling correlates with a higher incidence of ascites and shorter overall survival among patients, demonstrating that VEGF-A signalling not only promotes angiogenesis but also supports tumour growth directly. Significantly, the research implies that simultaneous dual targeting of VEGFR2 and PI3K/mTOR pathways has the potential to result in synergistic antitumor effects, boosting treatment efficacy and potentially reversing ascites accumulation. This reinforces a paradigm shift in considering anti-VEGF-A treatments as being not only anti-angiogenic, but also as inhibitors of tumour cell growth through their action on the AKT/mTOR pathway, hence providing a promising avenue for better therapeutic approaches to ovarian cancer.

PI3K inhibitors + EGFR inhibitors

Research suggests that the epidermal growth factor receptor (EGFR) is expressed in ovarian cancer, but agents targeting this are not as well effective as a single agent due to the activation of the alternative PI3K/AKT/mTOR pathway.[43] So, in a study, researchers aimed to overcome this resistance mechanism by combining EGFR inhibitors (erlotinib and gefitinib) and PI3K/AKT/mTOR pathway blockers (ZSTK474 and sirolimus) in ovarian cancer primary cell cultures.[45] ZSTK474 and EGFR inhibitors show synergism whereas combination with sirolimus is less active. At higher concentrations, the combination of EGFR and PI3K inhibitors shows antagonistic effects. It indicates that there might be a biologically optimal dose above which activity is lost.

Monotherapy targeting EGFR fails to suppress the compensatory signalling through other receptor tyrosine kinases – including HER2, HER3, IGFR, and c-MET. The resulting receptor heterodimerization provides alternative activation of the PI3K-Akt cascade, representing a

key resistance mechanism to single-agent EGFR inhibition.[46] Thus, inclusion of other agents like multi targeting HER inhibitors (e.g. lapatinib) against such PI3K compensatory pathways may have added effects.

Monotherapy targeting EGFR also results in increased STAT 3 phosphorylation. By adding a small molecule inhibitor of JAK, STAT 3 phosphorylation can be inhibited, which further produces a synergistic effect with the PI3K/AKT/mTOR pathway.[47]

CONCLUSION

The PI3K/AKT/mTOR signalling pathway is a central component of ovarian cancer pathogenesis, with common genetic changes in critical regulatory molecules. Numerous classes of PI3K pathway inhibitors have shown therapeutic activity in preclinical models and clinical trials. Shortcomings such as acquired resistance, toxicity, and activation of compensatory survival pathways make it necessary to initiate combination strategies that are rational.

New therapeutic strategies include combining PI3K inhibitors with other molecularly targeted drugs. Specific instances include co-treatment with PARP inhibitors to counteract DNA repair pathways, MEK inhibitors to counteract compensatory signalling pathways, and immunotherapeutic drugs to boost antitumor immune responses. Also, combinations with cytotoxic chemotherapy or vascular-targeting agents have demonstrated enhanced efficacy in certain molecular subgroups of ovarian cancer, notably in phenotypes of treatment-resistant disease.

Future therapeutic strategy should focus on biomarker-directed patient stratification and combination protocol optimization. Definition of predictive molecular signatures and resistance mechanisms will be imperative in tailoring treatment strategies. As our knowledge of PI3K pathway biology in ovarian cancer remains to grow, these targeted therapy strategies hold great promise for enhancing clinical management and patient outcomes for this refractory malignancy. Continued translational research activity is still necessary to achieve the full potential of these new treatment paradigms.

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