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REVIEW

Profile of erlotinib and its potential in the treatment of advanced ovarian carcinoma

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Abstract: The epidermal growth-factor receptor (EGFR) is overexpressed in the majority of epithelial ovarian cancers and promotes cell proliferation, migration and invasion, and angiogenesis, as well as resistance to apoptosis. This makes EGFR an attractive therapeutic target in this disease. A number of strategies to block EGFR activity have been developed, including small-molecular-weight tyrosine kinase inhibitors such as erlotinib. Erlotinib has been evaluated as a single agent in recurrent ovarian cancer, as well as in combination with chemotherapeutic agents in the first-line and recurrent settings, and in combination with the antiangiogenic agent bevacizumab in the recurrent setting, as well as in the maintenance setting after completion of first-line chemotherapy. Unfortunately, erlotinib has shown only minimal efficacy as a single agent, and it has not enhanced the effects of chemotherapy or bevacizumab when combined with these agents. Ongoing and future studies of erlotinib and other agents blocking EGFR will need to define mechanisms resulting in resistance to such interventions, and to validate biomarkers of response to identify patients most likely to benefit from such approaches.

Keywords: ovarian cancer, epidermal growth factor, epidermal growth-factor receptor, erlotinib, tyrosine kinase inhibitor

Introduction

Ovarian cancer is the fifth-leading cause of death in women in Canada, the US, and Europe. The majority of patients, except those with surgically resected disease of low stage and grade, have a need for effective postoperative systemic treatment.[1,2] Platinum containing combination chemotherapy has been standard for nearly two decades, and paclitaxel plus carboplatin has become the most widely accepted first-line regimen on the basis of several randomized trials.[3–6] Despite the efficacy of the combination of platinum/paclitaxel chemotherapy in advanced ovarian carcinoma, over 75% of patients with stage III/IV disease ultimately relapse and die from their disease. Treatment after relapse is dependent upon initial response to therapy and the interval between initial therapy and relapse for platinum-sensitive patients. This usually involves either carboplatin as a single agent, or in combination with paclitaxel, gemcitabine, or liposomal doxorubicin for platinum-sensitive disease. For platinum-resistant patients, this usually involves treatment with single-agent topotecan, doxorubicin (free or liposome-encapsulated), etoposide, gemcitabine, melphalan, or consideration of investigational agents.[7]

EGF and EGFR biology and role in ovarian cancer

New therapies with a novel mechanism of action with activity in this disease setting are clearly needed. Recently, attention has turned from classical cytotoxic agents to

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those new drugs that target molecular pathways of relevance in malignancy. One such molecular target is the epidermal growth-factor receptor (EGFR). EGFR is one of four known related members of a family of growth-factor receptors that are important mediators of cell growth, differentiation, and survival: human epidermal growth factor receptor type 1 (HER1; EGFR or ErbB1), HER2 (*neu* or ErbB2), HER3 (ErbB3), and HER4 (ErbB4). EGFR and its ligands, epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α) are important in cell proliferation, as well as motility, adhesion, invasion, survival, and angiogenesis.[8] Structurally, the EGFR family consists of an extracellular ligand-binding domain, a single transmembrane-spanning region, and an intracellular region containing the kinase domain (Figure 1).

More than 30 ligands that bind to the EGFR family in humans have been identified, including EGF and EGF-like ligands, TGF-α, and heregulins (also known as neuregulins).[9] The EGFR binding partner appears to depend on several properties. These include the proportion of EGFR family members in the membrane, as well as the type and proportion of ligand,[10,11] and cell lineage. EGF and TGF-α are the main endogenous ligands for EGFR. EGFR is activated upon ligand binding, which results in a conformational change in the extracellular domain, leading to homo- or heterodimerization with another EGFR family member, activation of tyrosine kinases, followed by receptor autophosphorylation and activation and propagation of signaling cascade, promoting growth. The major signaling pathways activated by EGFR dimerization intracellularly are the Ras/Raf/mitogen-activated protein kinase pathway, which regulates specific intranuclear transcription factors, thus inducing cell migration and proliferation, the signal transducer and activator of transcription (STAT) proteins pathway, which induces oncogenesis and tumor progression mainly through constitutive activation of STAT-3 and STAT-5, the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which regulates cell growth, apoptosis resistance to chemotherapy, as well as tumor invasion and migration, and the Src kinase pathway, which plays a fundamental role in the regulation of cell proliferation, migration, adhesion, and tumor angiogenesis (Figure 1).[12–14]

EGFR family members can also be activated by other signaling proteins independently of addition of exogenous EGFR ligands. These include other receptor tyrosine kinases (RTKs), such as the insulin-like growth factor-1 receptor (IGF-1R)[15,16] and tyrosine kinase receptor B,[17] as well as other types of receptors, such as G protein-coupled receptors (GPCRs),[18] the leptin receptor,[19] and adhesion proteins, such as E-cadherin[20] and integrins.[21] While the details of EGFR

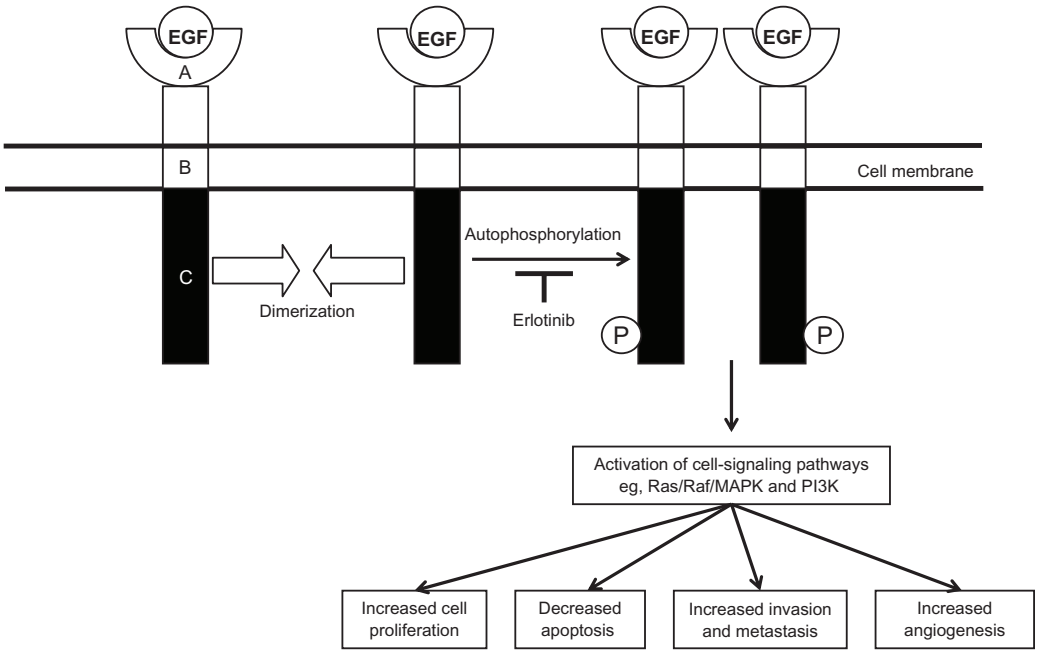

Figure 1 Epidermal growth factor (EGF) receptor structure.
Notes: Ligand binding of EGF leads to receptor dimerization, resulting in receptor autophosphorylation. This results in activation of a number of downstream signaling pathways. Autophosphorylation of the receptor is blocked by erlotinib. A, extracellular ligand-binding domain; B, transmembrane-spanning domain; C, intracellular domain containing the kinase domain; P, phosphorylation group.
Abbreviations: MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositide 3-kinase.

transactivation upon cross talk are not yet fully elucidated, transactivation has been shown to occur by a variety of mechanisms. There is evidence that EGFR can be transactivated by IGF-1R by direct binding.[22] Additionally, EGFR transactivation by GPCR has been shown to occur intracellularly, such as by activation of Src upon GPCR stimulation,[23] as well as extracellularly, such as by GPCR activation by gastrin-releasing peptide.[24] Lysophosphatidic acid (LPA) GPCR-induced ectodomain shedding of proheparin-binding EGF also activates EGFR.[25] LPA-mediated signaling is of particular importance in ovarian cancer, as abnormalities in LPA metabolism and function likely contribute to initiation and progression of ovarian cancer.[26–28] Additionally, tyrosine kinase receptor B may also play a role in ovarian cancer, as its activation has been shown to enhance migration and proliferation and to suppress anoikis in human ovarian cancer cells.[17,29]

EGFR is widely expressed in the surface of mammalian epithelial cells, fibroblasts, gliocytes, keratinocytes, and other cell types. Using an *EGFR* gene-knockout mouse model, it has been demonstrated that EGFR plays a physiologically favorable role during embryonic and postnatal development.[30–32] The EGF pathway is also critical in the control of ovulation. Luteinizing hormone induction of EGF-like growth factors and activation of EGFR signaling is essential for ovulation of mature oocytes.[33,34]

EGFR expression, mutation, and dysregulation

EGFR plays a pivotal role in tumorigenesis, and its expression strongly affects the outcomes of cancer patients in the clinic.[9] Overexpression of EGFR and its ligands leads to malignant transformation.[35] EGFR expression reported by various groups in malignant ovarian tumors appears to be highly variable, with expression detected by immunohistochemistry (IHC) ranging from 4% to 100%.[36–44] These differences are likely secondary to differences in reagents, experimental procedures, and study design.[36] In relation to the development of ovarian cancer, EGFR and its ligands are important in regulating the growth of the ovarian surface epithelium. Alterations of the receptor and its ligands result in a disruption in normal growth-regulatory pathways.[36] The presence of both TGF-α and EGFR in ovarian cancer cells suggests that an autocrine growth pathway may be implicated.[45] Accumulating evidence suggests dysregulation of EGFR may contribute to the malignancy of ovarian and other tumors through promotion of cell proliferation, migration and invasion, and angiogenesis, as well as resistance to apoptosis.[46–49] EGFR has also been found to act as a strong prognostic indicator in ovarian cancers, with increased expression being associated with reduced recurrence-free or overall survival (OS) rates.[50–52] Berchuck et al demonstrated that in ovarian cancer specimens with EGFR expression, survival was significantly reduced compared to EGFR-negative specimens, and patients without EGFR expression had a median survival of 40 months compared to 26 months in patients with EGFR-expressing tumors.[53]

The *EGFR* gene is mapped to chromosome 7 (7p12.3–p12.1). It consists of 28 exons and spans over 190 kb. *EGFR* gene amplification or protein overexpression occurs across all epithelial ovarian cancer histotypes.[54,55] Increased EGFR expression has been associated with high tumor grade,[41,54,56] high cell-proliferation index,[41] aberrant p53 expression,[41] and poor patient outcome.[41,56] The expression of EGFR, phosphorylated AKT, or phosphorylated ERK does not show any significant association with histological subtypes. However, overexpression of pAKT is correlated with progression-free survival (PFS) in ovarian cancer patients, based on their stage of disease and the degree of tumor differentiation.[57]

Polymorphisms of EGFR may affect the biology of ovarian cancer. Araújo et al[58] examined the effect of the A61G polymorphism (substitution of G for A at position 61). They found a decreased risk for developing ovarian cancer in the GG carriers compared to the AA carriers (odds ratio 0.46, confidence interval 0.25–0.81; $P = 0.010$). Garcia et al reported an association with response to lapatinib and a polymorphism in EGFR exon 20 (2361 G > A, Q787Q).[59]

The most common EGFR mutation is the type III deletion mutation (EGFRvIII) characterized by elimination of exons 2–7, causing an in-frame deletion of 801 base pairs in the extracellular domain coding sequence, which frequently occurs in malignant gliomas, breast cancer, non-small-cell lung cancer and other types of cancer.[60,61] The truncation of extracellular domain leads to constitutive activation of the receptor.[62] These activating mutations of EGFR are found exclusively in tumor cells. This type of alteration thus constitutes an optimal target for cancer therapy, and various medical agents have been developed and undergone clinical trials. With respect to ovarian cancer, studies assessing EGFRvIII expression show conflicting results. Moscatello et al demonstrated that EGFRvIII alteration was present in 73% (24/32) of ovarian carcinomas.[63] Lassus et al were unable to detect such mutations in EGFR in serous ovarian carcinoma.[41] Steffensen et al were also unable to detect such mutations. None of the tissues from 225 patients with normal, benign, borderline, or malignant ovarian cancers were positive for

the EGFRvIII mutation, either at the mRNA level or at the protein level.[64] The consensus at this time is that EGFRvIII mutations are rare in ovarian cancer and do not contribute significantly to the malignant phenotype in this disease.

Targeting EGFR in ovarian cancer

While several strategies have been developed to block EGFR activity, two types of inhibitors are currently used in the clinic: (1) monoclonal antibodies, and (2) small-molecule tyrosine kinase inhibitors (TKIs).[48,65] The focus of this paper will be on the small-molecular-weight TKI erlotinib (OSI-774, R 1415, CP 358774, NSC 718781; Tarceva®).

Erlotinib is an HER1/EGFR TKI. It is a quinazolinamine with the chemical name *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine. Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4 \cdot HCl$ and a molecular weight of 429.90[66] (Figure 2).

Mechanism of action

Erlotinib is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase.[66] Erlotinib inhibits the human EGFR tyrosine kinase with an IC_{50} of 2 nM (0.786 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumor cells, with an IC_{50} of 20 nM (7.86 ng/mL).[66] This inhibition is selective for EGFR tyrosine kinase in assays of isolated tyrosine kinases, and cellular assays. Erlotinib inhibits EGF-dependent proliferation of cells at submicromolar concentrations and blocks cell-cycle progression in the G_1 phase.

Erlotinib reversibly binds to the adenosine triphosphate-binding site of EGFR and completely inhibits autophosphorylation by EGFR tyrosine kinase. This results in blockage of downstream EGFR signal-transduction pathways, cell-cycle arrest, and inhibition of angiogenesis. However, the mechanism of clinical antitumor action of erlotinib is not fully characterized.[66]

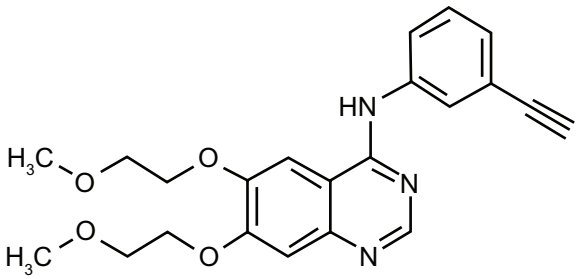

Figure 2 Erlotinib – chemical structure.
Notes: Chemical name, *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride; United States Adopted Name, erlotinib hydrochloride; other names, NSC 718781, CP-358, OSI-774; molecular formula, $C_{22}H_{23}N_3O_4$; molecular weight, 393.4 (free base).

Erlotinib is administered orally. It is absorbed slowly, with peak plasma concentrations occurring 3–4 hours after dosing, with a mean bioavailability of 60%. Bioavailability is significantly improved by administration with food (to approximately 100%) with the mean area under the curve (AUC) increasing by approximately 33% when given with food.[66] The increase in bioavailability from administration with food is substantial and increases the risk of drug-related side effects; therefore, erlotinib should be given on an empty stomach. Time to reach steady-state plasma concentration is 7–8 days, and its half-life is about 36 hours. Erlotinib is metabolized in the human liver primarily by cytochrome P450 (CYP)3A4 but also by CYP1A2, and to a minor extent by CYP2C8 (66). Extrahepatic metabolism by CYP3A4 in the intestine, CYP1A1 in the lung, and CYP1B1 in tumor tissue is thought to contribute to the metabolic clearance of erlotinib. Excretion is predominantly via the feces (83%), with renal elimination of the drug and metabolites accounting for 8% of the administered dose. Less than 2% of a dose is eliminated as unchanged drug.[66]

Clinical trials of EGFR inhibition in ovarian carcinoma

Erlotinib single-agent trials

A single-arm phase II study was conducted by Gordon et al to evaluate erlotinib (150 mg/day) as a treatment option in 34 patients with platinum-resistant or -refractory ovarian cancer.[67] All tumors were confirmed to be EGFR protein expression-positive by IHC. Erlotinib demonstrated limited activity for ovarian cancer patients, with an objective response rate of 6% (all partial responses [PRs]), and an additional 14 patients had stable disease that lasted longer than 2 months. Median time to disease progression was 62 days, and the median survival was 8 months. Survival was significantly longer in women who developed a rash.[67]

Erlotinib in combination with chemotherapy

There is preclinical evidence suggesting that EGFR TKIs potentiate the antitumor effects of cytotoxic agents, including carboplatin.[68] Preliminary evidence in an in vitro fibroblast model indicates that EGFR TKIs may beneficially modulate drug resistance, and that EGFR may be causal in the development of resistance to platinum.[69]

There have been several reports of studies in which standard chemotherapeutic agents were combined with erlotinib in the treatment of ovarian carcinoma. A phase Ib study

Table 1 Clinical trials of erlotinib in ovarian cancer

Study reference	Phase	Number of patients	Therapy	Patient population	Response
Gordon et al[67]	II	34	Erlotinib 150 mg/day	Platinum-refractory HER1/EGFR-positive	RR – 6% (2/34) PR – 6% (2/34)
Vasey et al[70]	Ib	23	Carboplatin AUC 5 + docetaxel 75 mg/m^2 q3 weekly Erlotinib 50–100 mg/day	First-line therapy	RR – 52% (12/23) CR – 22% (5/23) PR – 30% (7/23)
Blank et al[72]	II	56	Carboplatin AUC 6 + paclitaxel 175 mg/m^2 q3 weekly Erlotinib 150 mg/day	First-line therapy	**Pathological CR** Optimal cytoreduction – 29% (8/28) Suboptimal cytoreduction – 13% (3/23)
Hirte et al[73]	II	50	Carboplatin AUC 6 + paclitaxel 175 mg/m^2 q3 weekly Erlotinib 150 mg/day	Recurrent platinum-sensitive or -resistant disease Up to 2 prior therapies	**Platinum-sensitive** RR – 57% CR – 10% (3/33) PR – 47% (14/33) **Platinum-resistant** RR – 7% (1/17) CR – 0% PR – 7% (1/17)
Nimeiri et al[74]	II	13	Bevacizumab 15 mg/kg q3 weeks Erlotinib 150 mg/day	Platinum-resistant or platinum-refractory	RR – 15% (2/13) CR – 7.5% (1/13) PR – 7.5% (1/13)
Chambers et al[75]	II	40	Bevacizumab 10 mg/kg q2 weeks Erlotinib 150 mg/day	Platinum-resistant or platinum-refractory	RR – 23% (9/39) CR – 3% (1/39) PR – 20% (8/39)
Vergote et al[76]	III	835	Maintenance postchemotherapy Erlotininb 150 mg/day versus placebo	Post-first-line chemotherapy	**Overall survival** Erlotinib – 51 months Placebo – 59 months (P = 0.60) **Progression-free survival** Erlotinib – 12.7 months Placebo – 12.4 months (P = 0.90)

Abbreviations: RR, response rate; CR, complete response; PR, partial response; AUC, area under the curve; HER1, human epidermal growth factor receptor type 1; EGFR, epidermal growth-factor receptor; q, every.

of erlotinib in combination with carboplatin (AUC 5) and docetaxel (75 mg/m^2), followed by erlotinib (75 to 100 mg/day orally) every 21 days in women with chemotherapy-naive ovarian cancer demonstrated an objective response rate of 52% (12/23 patients).[70] EGFR aberration or positivity was not an inclusion criterion. The response rate of the erlotinib + docetaxel + carboplatin combination therapy was slightly lower than that of the docetaxel + carboplatin therapy previously conducted by the same group (52% versus 59%).[71]

In a phase II study of newly diagnosed patients with advanced ovarian cancer, 56 patients were treated with paclitaxel (175 mg/m^2) and carboplatin (AUC 6) every three cycles, plus erlotinib (150 mg daily). The objective was to increase the pathologic complete response rate (pCR); however, this was achieved in only eight of 28 patients (29%) after optimal cytoreduction (<1 cm residual disease) and three of 23 patients (13%) who were suboptimally debulked. Tumor specimens were analyzed for EGFR amplification in 20 patients, but no statistically significant correlation was observed between amplification status and response. The addition of erlotinib to carboplatin–paclitaxel did not improve the likelihood of achieving a pCR compared to historical controls.[72]

Hirte et al investigated the effect of adding erlotinib (150 mg/day) to carboplatin chemotherapy (AUC 5 every 21 days) in 50 ovarian cancer patients who previously had received platinum-based drugs, with 33 in the platinum-sensitive arm and 17 in the platinum-resistant arm.[73] In the platinum-sensitive arm, there were three (10%) complete responses (CRs) and 14 (47%) PRs, for an overall response rate (ORR) of 57%. In the platinum-resistant arm, there were no CRs and one PR, for an ORR of 7%. For platinum-sensitive patients with EGFR-positive tumors, there were twelve responses (60% ORR), and in the platinum-resistant arm, the only responding patient was EGFR-positive.[73] The combination could be safely administered, and the toxicities were those expected from this combination. However, there was no evidence that erlotinib

enhanced the response rate in the platinum-sensitive patients, nor was erlotinib able to reverse resistance to platinum in the platinum-resistant arm.[73]

Erlotinib in combination with targeted agents

Erlotinib has also been tested in combination with the vascular endothelial growth factor-neutralizing antibody bevacizumab (Avastin) in a phase II trial of patients with recurrent or refractory ovarian cancer.[74] Patients were treated with bevacizumab (15 mg/kg intravenously) every 21 days, and with erlotinib (150 mg/day) orally continuously. EGFR aberration or positivity was not required for inclusion in the study. EGFR status was examined by EGFR positivity via IHC and activating mutations in exons 19 and 21 via polymerase chain reaction amplification and sequencing. The ORR was 15% (2/13 patients, one CR and one PR).[74] No EGFR mutations were detected, and one patient demonstrated EGFR positivity, but this patient was unresponsive to erlotinib and bevacizumab therapy. The addition of erlotinib did not appear to be associated with an improvement over bevacizumab therapy alone, and there were two incidents of fatal gastric perforations with the combination.[74]

Chambers et al treated 40 patients with platinum-refractory or -resistant recurrent ovarian cancer with erlotinib (150 mg/day orally) and bevacizumab (10 mg/kg intravenously) every 2 weeks until disease progression.[75] Nine (23.1%) of 39 evaluable patients had a response (median duration of 36 weeks, one CR and eight PRs), and ten (25.6%) patients had stable disease, for a disease-control rate of 49%. The authors concluded that bevacizumab plus erlotinib in this patient population was clinically active and well tolerated, but that erlotinib did not appear to contribute to efficacy.[75]

Erlotinib as maintenance therapy

Recently, a phase III clinical trial randomizing patients to erlotinib versus observation following first-line therapy with no evidence of disease progression was completed.[76] A total of 835 patients received six to nine cycles of platinum-based chemotherapy every 3 weeks, and were eligible if they showed no signs of disease progression at the end of chemotherapy. They were then randomly assigned into two arms: one group received 150 mg of maintenance erlotinib daily for 2 years, and the other group was observed. As a secondary analysis, IHC and fluorescence in situ hybridization (FISH) analyses were conducted in 330 patients to determine the predictive value of IHC and FISH for EGFR and EGFR mutations. The primary end point was PFS, with secondary end points of OS, quality of life, and complications. After 24 months of accrual, there were not enough events to reach the study's end point, and patient accrual was stopped. PFS was 12.7 months for patients treated with erlotinib and 12.4 months for observed patients ($P = 0.916$). OS for the two groups was 51 months for patients treated with erlotinib and 59 months for observed patients ($P = 0.603$). Subsequent analyses of the data looked at the relationship between EGFR-mutation status and PFS. Among patients treated with erlotinib, 318 had mutations in EGFR, KRAS, NRAS, BRAF, or PI3KCA; however, there was no significant relationship between PFS and the development of rash during erlotinib treatment, and no differences based on International Federation of Gynecology and Obstetrics stage, age, or response at the end of first-line chemotherapy. There were no subgroups identified that might benefit from erlotinib maintenance therapy after first-line chemotherapy for ovarian cancer.[76]

Resistance mechanisms

An understanding of the mechanisms leading to resistance of EGFR inhibitors could help patients likely to respond to therapy and could help identify other agents that could be combined with such inhibitors. A number of mechanisms may allow cancer cells to become resistant to EGFR inhibitors. Resistance may be present at the onset of treatment (intrinsic) or may develop over time (acquired).[77] At a molecular level, mechanisms of resistance to EGFR therapy include production of EGFR-activating ligands, receptor mutations, constitutive activation of downstream pathways, and activation of alternative signaling pathways.[77,78] The downstream cellular signals transduced by EGFR are mediated by several other kinases whose activity is usually dependent on activation by EGFR (Figure 1). If any of these enzymes become mutated, this can lead to a constitutively active pathway. Regardless of EGFR blockade, this constitutively active pathway will remain active, which can result in an EGFR inhibitor-resistant phenotype.

Other mechanisms proposed include resistance to autophagic cell death upon increased EGFR expression via stabilization of the facilitated glucose transporter sodium/glucose cotransporter 1 (SGLT1)[79] and inflammation.[80] SGLT1 can transport glucose upstream of a glucose gradient, enabling cells to accumulate higher glucose concentrations than their environment.[79] Since the increased SGLT1 stability is dependent on EGFR expression and not its activity,[79] agents that target EGFR activity but not its expression are likely to be ineffective. Another potential mechanism of EGFR-inhibitor resistance is inflammation, which allows

cancer cells to induce phosphorylation of mitogen-activated protein kinase, allowing a bypass of EGFR activation.[80] The sequence or timing of multidrug administration may be important in how efficacious drug combinations are. Proliferation of an esophageal squamous epithelial cancer cell line possessing autocrine EGFR activity was either inhibited or enhanced depending on whether a cytotoxic drug (platinum derivative or taxane) was administered before or after an EGFR inhibitor.[81] Although many of these mechanisms have been described in other cancer types, the relevance for these mechanisms in ovarian cancer is currently not clear.

Discussion

There are a number of factors that may explain the relative lack of activity of erlotinib in ovarian cancer. There is a lack of validated biomarkers for response to such TKIs, and to date the only known predictors of response are the activating mutations in the EGFR kinase domain, and these do not appear to play a significant role in the biology of ovarian cancer. Although the EGFR pathway appears to play an important role in the biology of ovarian cancer, in particular driving cellular processes linked to ovarian tumor development, tumor-cell survival, and metastasis, it is not clear how this can best be taken advantage of for therapeutic benefit. As a single agent, erlotinib has demonstrated minimal therapeutic activity in the first-line setting. Even though EGFR is overexpressed in most ovarian cancers, it does not appear that blocking signaling of the receptor alters sensitivity to platinum-based chemotherapy. In the first-line setting, combining erlotinib with platinum-based chemotherapy resulted in high response rates, although it is not clear in these nonrandomized studies whether these agents enhanced the activity of the chemotherapy or not. This also reflects the experience in the recurrent-disease setting. Nor does erlotinib appear to have efficacy in maintenance of response postchemotherapy in the first-line setting. And lastly, combining erlotinib with the angiogenesis inhibitor bevacizumab does not appear to have enhanced efficacy compared to bevacizumab alone.

One key goal in applying erlotinib to ovarian and other cancers will be to identify patients most likely to benefit from such a targeted therapy and to validate biomarkers of response.[82,83] Clearly, a better understanding of in vivo efficacy, improved predictive biomarkers of response, and an understanding of the molecular resistance pathways for EGFR antagonists is needed in ovarian cancer. Given that concurrent activation of multiple signaling pathways and pathway cross talk occurs in tumor cells, inhibition of multiple pathways has been proposed as a strategy to improve the impact of targeted therapeutics.[82] As such, the latest approaches in clinical trials, in a variety of tumors, are to combine the EGFR antagonists with inhibitors of other related or downstream signaling pathways. The impact on biologic endpoints in vivo will be critical to assess the mechanisms of action of these combined therapies. Ongoing research continues to identify new and more effective inhibitors of EGFR activity and novel approaches to target antitumor therapies via EGFR. Exploiting EGFR to target and deliver drugs or imaging agents to tumor cells shows promise in preclinical models.[84] Although the clinical application of EGFR antagonists and EGFR-targeted therapies to ovarian cancer treatment has not kept pace with their application in other tumors, such as lung and colorectal cancers, what is learned from using these agents in other diseases could well be applied to the benefit of ovarian cancer patients.

Disclosure

The author reports no conflicts of interest in this work.

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