Epidermal Growth Factor Receptor Inhibitors for the Treatment of Epithelial Ovarian Cancer

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The majority of patients with ovarian cancer, especially those who present with stages IIIC and IV, will relapse soon after completion of platinum-based induction treatment. It is imperative to find ways to improve and/or enhance the efficacy of induction and to prolong the duration of the first remission. The epidermal growth factor receptor (EGFR) family has been exploited, and currently, three agents that directly target this group of receptors are in use in the treatment of colorectal, non-small-cell lung and breast cancers. EGFR and HER2/neu are overexpressed in a significant percentage of epithelial ovarian cancers. Thus, it would be reasonable to explore directly targeted therapy in ovarian cancer. Numerous investigational trials involving a variety of EGFR inhibitors in ovarian cancer are ongoing. Our institution has an active phase II clinical study that seeks to define the role of erlotinib (Tarceva) in potentiating first-line chemotherapy, and to determine whether the drug offers a significant contribution as maintenance therapy. It is hoped that data from these and other studies will help investigators to understand more clearly the biology of ovarian cancer and to delineate the role of EGFR inhibitors in the management of ovarian cancer.

During the past year, the US Food and Drug Administration approved for use in cancer treatment both a small-molecule inhibitor (gefitinib, ZD1839, Iressa) of the epidermal growth factor receptor (EGFR) and a monoclonal antibody directed against its extracellular domain (cetuximab, C225, Erbitux). Gefitinib was approved as a single agent for the treatment of lung cancer, with sustained responses observed in slightly more than 10% of all patients with non-small-cell lung cancer enrolled in those trials. Such responses may be especially dramatic in a recently identified subset with gain-of-function somatic mutations in the tyrosine kinase (TK) domain of the EGFR gene.[1] Cetuximab showed clear activity against colorectal cancer that was resistant to irinotecan (Camptosar), particularly when given together in combination with irinotecan. Three years earlier, an antibody directed against another member of the EGFR family, trastuzumab (Herceptin), was approved for the treatment of metastatic breast cancer characterized by the overamplification of the erbB2 (HER2/neu) gene. These developments, arriving nearly 30 years after the isolation and delineation of the biologic properties of the human epidermal growth factor by Stanley Cohen and his group,[2] are an affirmation of the importance of such growth factors and receptors in ensuring proliferation and survival of epithelial neoplasms. From the outset, studies of small-molecule inhibitors focused on cancers of the lung and the aerodigestive tract, whereas the antibodies underwent preferential development against colorectal cancer, and to a lesser extent against cancers of head and neck origin. Excellent reviews on the background and clinical experience with these agents have been published.[3-5] Although there has been persistent interest and often some hints of activity in tumors arising from gynecologic organs, the development of therapeutic strategies using these agents against gynecologic cancers has lagged behind those of the above noted sites. In order to stimulate interest and provide a road map for further clinical development in this area, we review here the rationale and possible role of such agents in the treatment of ovarian cancer, the variety of trials that are ongoing (including an overview of the rationale for our own trial with erlotinib [OSI-774, Tarceva] added to first-line chemotherapy), and the types of compounds being tested. Finally, we shall consider future directions for these agents in the treatment of ovarian cancer.

Ovarian Cancer Treatment Overview Currently, platinum-based chemotherapy is effective as induction therapy for ovarian cancer, with only 1 of 10 patients relapsing during treatment. However, the majority of patients, such as those who present with disease stages IIIC and IV, will relapse soon after cessation of the induction regimen. A study by Markman[6] clearly showed that the median time to relapse, even for patients deemed to be in clinical complete response, is only 21 months in patients assigned to receive three more doses of paclitaxel, and 29 months for those that had 1 year of maintenance treatment with paclitaxel administered every 4 weeks. Prior studies have suggested that the progression-free survival is only about 16 months if patients had suboptimal debulking, and about 24 months for optimally debulked stage III patients. It is important,
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therefore, to look at ways to improve the efficacy of induction, and it is also a major unmet need to
find drugs that prolong the duration of first remission. Despite the existence of several second-line
drugs that induce responses in patients who experience recurrence, a trial of consolidation with
intraperitoneal (IP) cisplatin was closed early short of its accrual goals with only a trend for fewer
recurrences,[7] while either an IP radioimmunoconjugate[8] or continued treatment with four cycles
of topotecan (Hycamtin) or epirubicin (Ellence) has not resulted in an improved outcome compared
to observation.[9-11] Altretamine (Hexalen) consolidation for 1 year has been used only in a trial
without a control.[12] Until the recent demonstration that the combination of paclitaxel and
carboplatin led to improved survival when used as second-line therapy and compared to carboplatin
by itself,[13] these second-line drugs had an uncertain effect on survival. Another exception that has
emerged relates to a recent trial of topotecan vs pegylated liposomal doxorubicin (Doxil), where an
update showed a survival advantage with the latter agent in a patient population that included both
platinum-sensitive and platinum-resistant patients.[14] In platinum-resistant patients (those
relapsing within 6 months of completing the platinumbased induction), all these secondline drugs are
generally less active, and chronic maintenance is likely to be desirable.[15] Noncytotoxic drugs have
been considered an excellent choice for consolidation therapies because one would not expect
long-term toxicity issues. Tamoxifen has often been used, but only recently has a randomized study
been initiated by the Gynecologic Oncology Group (GOG). Inhibitors of EGFR are among the potential
candidates for use in consolidation, but such studies await experience against established disease
and more extensive delineation of the role of EGFR in ovarian cancer. In first-line treatment, one
might also consider whether modulation with a "targeted compound" might enhance the results of
chemotherapy. Presently, the GOG is planning to evaluate the effect of an antibody to the vascular
endothelial growth factor (VEGF) bevacizumab (Avastin) when added to paclitaxel and carboplatin vs
chemotherapy alone in a future phase III study. EGFR inhibitors will have to wait for another
generation of first-line trials and additional data before upfront phase III studies can be designed.

**EGFR and Ovarian Cancer**

Gonadotropin and steroid hormones have been implicated in ovarian tumorigenesis,[16] and—as in other tumor types—coexist to a variable degree with EGFR-mediated
signaling. In fact, hormone receptors, as well as EGFR and HER2/neu are overexpressed in a
significant percentage of epithelial ovarian cancers.[17-21] Moreover, coexpression of both erbB1
and erbB2 (HER2/neu) is common in ovarian cancer.[22-23] In preclinical studies, antisense
suppression of EGFR affects proliferation and tumorigenicity of ovarian cancer cells.[24-25]. More
recently, an emerging relationship between MUC genes and expression of EGFR has been described.
Such a relationship has generated some interest, and further, has been deemed worth pursuing
against mucinous histologies. In general, mucinous tumors of ovarian origin tend to have an inferior
chemosensitivity relative to the more common papillary serous histologies. Other histologies such as
endometrioid and clear cell also reflect differences in biologic behavior and in gene expression.[16]

Mucins, produced by MUC genes, are complex proteins elaborated by many cell types, including
those of the gastrointestinal and respiratory tracts, to maintain cellular homeostasis in harsh
environments. Mucins have been implicated in the pathogenesis of many cancers, and are often
expressed in large concentrations and in different forms than their benign counterparts. Cancer cells
use mucins in much the same way as normal epithelia— for protection from adverse growth
conditions and to control the local molecular microenvironment during invasion (by simultaneously
disrupting existing interactions between opposing cells) and metastasis (by establishing new ligands
for interaction between the invading cell and the adjoining cells).[26] Many mucins contain domains
homologous to those of the epidermal growth factor (EGF) family, through which mucins (and the
cells that elaborate them) directly interact with EGFRs.[26] Mucins contribute to the regulation of
differentiation and proliferation of tumor cells, through ligand-receptor interactions (for example,
between MUC4 and EGFR2 [HER2/neu]) and signal transduction.[26] Through these interactions,
malignant cells can initiate signaling cascades to induce growth and differentiation. In some
instances, the EGF domains on mucins may act on EGFRs of the same cell, in an autocrine fashion.
For example, MUC4 mucin is aberrantly expressed in premalignant pancreas cells. The EGF-like motif
on MUC4 has been shown to make autologous receptor-ligand interaction with EGFR2, inducing a
signaling cascade that allows the cells to sustain differentiation and survival.[26] MUC2 and MUC5AC
are two target genes of EGFR ligands; upregulation occurs via concomitant activation of the
EGFR/Ras/Raf pathway.[27] Mucinous tumors, whether of gynecologic, gastrointestinal, or other
intra-abdominal origin, tend to have worse outcomes after platinum-based chemotherapy.[28-30]
These tumors have a distinct biology: They are prone to massive growth and extensive peritoneal
infiltration, have a propensity for metastasizing via the peritoneal route rather than the
hematogenous route, and tend to persist even after surgery and chemotherapy.[31]
Inhibitors: Phase I/II Experience in Ovarian Cancer
The following EGFR inhibitors are undergoing testing in ovarian cancer patients:

- **Trastuzumab**-This humanized monoclonal antibody directed toward the extracellular domain of HER2/neu has undergone formal testing in one trial in ovarian cancer conducted by the GOG. It initially generated great interest but ultimately yielded disappointing results: Not only was overexpression of HER2/neu in the disease considerably less frequent than initial estimates of 20% to 40%, but the antibody given as a single agent yielded very few responses.[32] Some evidence indicates that the incidence of HER2/neu overexpression increases during the course of ovarian cancer and is most common in patients who relapse with ascites.[33]

- **Pertuzumab (Omnitarg, 2C4)**- The effect of this humanized monoclonal antibody is to inhibit the dimerization of erbB1 and erbB2- thus, its effect may not be dependent on HER2/neu amplification.[34] In phase I/pharmacologic studies, one patient with ovarian cancer experienced an objective response lasting 9 months. Phase II trials sponsored by Genentech have been initiated in ovarian cancers that do not overexpress HER2/neu.

- **Anti-EGFR Antibodies**-Trials of anti-EGFR antibodies have also been initiated but not yet published. These include trials with the chimeric monoclonal antibody cetuximab, the humanized monoclonal antibody EMD72000, and the fully humanized monoclonal antibody ABX-EGF. In phase I studies of these agents, patients with ovarian cancer were enrolled and anecdotally some responses were noted, thus encouraging phase II studies. The GOG recently embarked on a phase II study of cetuximab on their "biologic" phase II queue. An EMD72000 sponsored phase II trial in ovarian cancer has been completed but not yet reported.

- **Gefitinib**-This agent is a quinazoline derivative that competes with adenosine triphosphate (ATP) in the binding pocket of its intracellular catalytic domain and thereby prevents phosphorylation and activation of EGFR TK activity. In a dose-escalation phase I and pharmacodynamic study,[35] 23 of 88 patients enrolled had ovarian cancer, but only one of the patients (receiving 300 mg/d) was still receiving treatment after 6 months. Grade 3/4 toxicities were experienced by five patients- three at 1,000 mg/d, and one each at 400 and 600 mg/d. Of note, EGFR signaling is a vital growth regulator in estrogen receptor (ER)-positive acquired tamoxifen-resistant breast cancer models, and preliminary studies showed that in ER-positive patients with breast cancer, high levels of HER2 did not preclude a response to gefitinib.[36] The GOG initiated a trial in ovarian cancer with this small-molecule inhibitor in patients who had failed other therapies within a separate queue of previously treated patients (any number of prior treatments but good performance status). The GOG investigators established new end points in order to identify activity beyond objective antitumor effects depending on Response Evaluation Criteria in Solid Tumors (RECIST) standards. A drug would be deemed to have encouraging activity if the percentage of patients not progressing at 6 months exceeded 30%. Although some evidence of antitumor effect was documented with gefitinib, it was not sufficient to support further study with the drug in patients with ovarian cancer. In other studies, however, gefitinib plus combination chemotherapy as second-line treatment for ovarian cancer demonstrated favorable response rates. A French phase II study involved the administration of gefitinib combined with paclitaxel and carboplatin as second-line therapy, with a resultant overall response rate of 25% in platinum-resistant patients and 71% in platinum-sensitive patients.[37] A German phase II study that evaluated gefitinib in combination with tamoxifen in platinum/taxane-refractory ovarian cancer patients demonstrated a 2.1% complete response rate, a 19.1% stable disease rate, and a 6-month survival rate of 56.6%.[38] A Greek phase I/II trial using gefitinib in combination with vinorelbine (Navelbine) and oxaliplatin (Eloxatin) as salvage treatment for advanced ovarian cancer resulted in three complete responses and two partial responses in the cisplatin-refractory group, and four complete responses and five partial responses in the cisplatin-sensitive group.[39]

- **Erlotinib**-Also a quinazoline, erlotinib has a similar mechanism of action to that of gefitinib. In phase I trials, responses were seen in several diagnostic categories, including patients with ovarian cancer. Accordingly, a trial was initiated by OSI Pharmaceuticals and published in abstract form[40]: 3 of 34 patients were noted to have partial responses after 150-mg/d treatment, with stable disease also noted in 3 others at 5, 5, and 6 months. Under
sponsorship by the National Cancer Institute, this agent will undergo additional studies in combination with chemotherapy. Interestingly, a recent translational study conducted in metastatic breast cancer patients who were treated with erlotinib demonstrated gene expression profile changes in a wide array of genes both in EGFR-positive and EGFR-negative tumors, suggesting that erlotinib has additional targets.[41] As discussed in the next section, our institution has been using this drug in combination with carboplatin and paclitaxel in the first-line setting for ovarian cancer. Currently, a European collaborative has demonstrated antitumor activity in a phase I study involving the administration of erlotinib in combination with docetaxel and carboplatin as first-line treatment for ovarian cancer.[42] A Canadian study of EGFR-overexpressing recurrent or metastatic endometrial cancer using erlotinib as a single agent has resulted in one partial response and three cases of stable disease, with tolerable toxicities.[43]

• **PKI 166**-This pyrrolopyrimidine compound also competes with the ATP binding site on EGFR TK in the nanomolar range, and at somewhat higher concentrations inhibits the autophosphorylation of HER2/neu, making it a dual inhibitor.[44] Three phase I studies have been performed with reversible transaminitis, diarrhea, and rash being dose limiting.

• **Lapitinib (GW572016)**-This compound is in development because of its ability to inhibit kinase activity, including that of erbB1, erbB2, ERK1, ERK2, and AKT, in the nanomolar range.[45] In phase I trials, the toxicities were not unlike those described above for PKI 166.[46-47]

• **EKB569 and CI-1033**-Both these drugs are irreversible inhibitors of erbB1 and erbB2, with a similar spectrum of toxicities as drugs described earlier, but their long-lasting effect on the receptors have led to more cautious and therefore more prolonged study in phase I. A phase I study of EKB569 has been conducted,[48] with diarrhea and rash as the most frequently reported adverse events. CI-1033 demonstrated some antitumor activity in patients with ovarian cancer,[49] and a formal phase II study enrolling 100 patients at three different dose levels has been carried out. The patient population was heavily pretreated, but some activity was observed, while tolerance varied with dose level; publication is awaited.[50]

• **E1a**-In addition to the above agents, E1a, a gene product of adenovirus type 5, has been found to downregulate HER2/neu and cause tumor regression in animal models. This occurs because the HER2/neu promoter has several positive elements that require the p300/CREB-binding protein coactivator proteins, which are inhibited by direct E1a interaction.[51] A recently completed phase I gene therapy clinical trial involving intraperitoneal delivery of E1A-lipid complex to patients with recurrent ovarian cancer overexpressing HER2/neu demonstrated safety and gene transfer but no evidence of efficacy.[52]

• **Summary**-This initial experience has provided the rationale for further exploration utilizing the strategies listed below:
  1. Phase II studies of monoclonal antibodies directed against EGFR alone and in combination with cytotoxic drugs, as well as with other "targeted drugs" such as the antibody targeting VEGF, bevacizumab.
  2. Phase II studies of TK paninhibitors of EGFR and HER2: Again, these have been performed or are ongoing and planned with agents that have a wider range of inhibition than gefitinib and erlotinib, such as CI-1033 and GW572061.
  3. Integration of erlotinib into first-line chemotherapy: understanding the possible potentiation of chemotherapy by this drug, and studying the contribution of maintenance therapy.

### Carboplatin, Paclitaxel, and Erlotinib as First-Line Therapy

Preclinical findings have suggested that interfering with EGFR signaling enhances the cytotoxic action of certain chemotherapeutic agents, and in particular, the platinum compounds. Evidence of this enhancement against cell lines and animal tumors provided the rationale for the first combination studies with trastuzumab in breast cancer.[53-55] Of all the chemotherapeutic drugs, however, enhancement of platinum-induced cytotoxicity is most prominent.[56-59] In spite of this preclinical rationale, the trials of combined chemotherapy and TK inhibitors in non-small-cell lung cancer were negative.[60-61] New information suggests that patients with receptor accumulating gain-of-function mutations in the TK domain of EGFR are most susceptible to TK inhibitors such as gefitinib.[1] Otherwise, these drugs have shown limited efficacy against other non-small-cell lung cancers despite EGFR expression. Nevertheless, the relevance of such findings to other cancers is
currently unknown. The rationale for the study of erlotinib added to first-line therapy of ovarian cancer (Figure 1) includes the following: (1) activity in preclinical and clinical studies noted in the preceding sections; (2) the fact that compared with lung cancer, ovarian cancer tissue is more often available after therapeutic intervention—therefore, samples obtained at reassessment may prove informative as to the nature of cells surviving treatment with chemotherapy and EGFR inhibition; and (3) the need for exploring better induction regimens and also maintenance therapy as initial treatment of advanced ovarian cancer. Accordingly, our trial was begun under sponsorship of the National Cancer Institute and has accrued 18 patients with stage III/IV ovarian cancer during its first year. All tumor specimens have had baseline determinations of EGFR and phosphorylated EGFR by immunohistochemistry. Patients proceeding to second-look laparotomy with disease presence are having repeat determinations and tissue frozen for additional determinations to verify the status of downstream signal transduction pathways.
Future Directions

Several issues need to be considered in the future use of these drugs, in relation to our growing appreciation for the biology of ovarian cancer. Future studies must take into account the following aspects of treatment: (1) Integration with other molecular-targeted therapies. Studies particularly conducted in breast cancer patients, but perhaps also reasonable in ovarian cancer, are seeking synergy of these drugs with hormonally directed agents such as tamoxifen. It has been
suggested that an increase in growth factor and cellular kinase signaling in breast tumors potentiates the ER pathway, which in turn reactivates growth factor signaling via both genomic and nongenomic activities, resulting in a stimulatory cycle that intensifies activity in the ER and EGFR pathways.[62] There is growing evidence that in breast cancer there is "cross-talk" between estrogen receptors and the EGFR family. In preclinical models of breast cancer, both EGFR and c-erbB2 mRNA and protein expression were increased in tamoxifen-resistant compared with wild-type MCF-7 cells. Phosphorylated EGFR/c-erbB2, EGFR/c-erbB3 were detected in tamoxifen-resistant cells in association with increased levels of phosphorylated extracellular-signal regulated kinase 1/2 (ERK1/2); treatment of tamoxifen-resistant cells with gefitinib or trastuzumab blocked c-erbB receptor heterodimer formation and phosphorylation, reduced ERK1/2 activity, and strongly inhibited cell growth.[63] Other preclinical breast cancer models also suggest that tamoxifen's agonist effects are mediated by EGFR/HER2, and that using growth factor pathway inhibitors might improve tamoxifen's benefit by eliminating its agonist effect.[64] As is being done in colorectal cancer, the GOG is planning to explore double targeting of angiogenesis (with bevacizumab) and EGFR (with cetuximab). Phase I studies of ACA-125 are under way. This murine anti-idiotypic monoclonal antibody that mimics CA-125 has, so far, been well tolerated and has induced appreciable Ab3 responses in ovarian cancer.[65] Additional combinations await both preclinical and clinical leads. (2) Integration with conventional anticancer therapies. Our study is exploring leads for the use of erlotinib in first-line treatment. We hope from this experience to also obtain a preliminary indication of whether it is reasonable to test this agent in consolidation chemotherapy. In addition, we seek to obtain some indication of antitumor effects associated with erlotinib-related toxic events such as rash. (3) Study of pharmacodynamics and validation of the target. In the future, it is likely that one will be able to obtain a molecular characterization of the various histologic cell types. It is important to delineate the role of EGFR pathways for each category. Indications that clear cell, mucinous tumors and endometrioid tumors are distinct from serous tumors in many molecular aspects suggest that this is fertile ground for future clinical and translational investigations.

Disclosures:
The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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