Commentary (Gibson): Targeting the Epidermal Growth Factor Receptor

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The epidermal growth factor receptor (EGFR) promotes the growth of different cell types and has been implicated in tumorigenesis. The EGFR comprises a family of four structurally similar tyrosine kinases with a complex link to downstream signaling molecules that ultimately regulate key cell processes. Anti-EGFR agents have been developed as promising therapeutic anticancer targets, and some have been recently approved for the treatment of non-small-cell lung cancer and colon cancer. The two anti-EGFR therapies with the greatest clinical application are monoclonal antibodies that block the binding of ligands to EGFR and small-molecule tyrosine kinase inhibitors that inhibit the binding of adenosine triphosphate to the internal tyrosine kinase receptor of EGFR. We attempt to give an overview of the EGFR function and biology, focusing on the most important clinical findings and applications of EGFR inhibitors in lung and head and neck cancer.

Saba and colleagues provide a summary of epidermal growth factor receptor (EGFR) and human epidermal growth factor (HER) family biology followed by a review of both preclinical and clinical experience with EGFR-targeted agents in both non-small-cell lung cancer (NSCLC) and squamous cell cancers of the head and neck (SCCHN). After describing the biology, the clinical focus of their article lists the design and outcomes of most of the phase I-III studies that involve monoclonal antibody (mAb) and tyrosine kinase inhibitor (TKI)-directed drugs either alone or in combination with chemotherapy or radiotherapy.

The article sets the stage for a discussion of why the efficacy of these therapies is limited when they are given alone or in combination with chemotherapy and radiotherapy. Pursuit of an explanation is leading to accumulating understanding of biologic mechanisms that enable selection of patients who will benefit most from these drugs. The promise is to enable enrichment of patient populations in order to include a higher fraction of responders in subsequent studies.

Promise Unfulfilled
One overriding conclusion from available clinical data is that, perhaps with the exception of the combination with radiotherapy, EGFR-targeted therapies for NSCLC and SCCHN are of limited clinical value as currently applied. Several theories address why, when given both as single agents and in combination with concurrent chemotherapy, the promise of these drugs is as yet unfulfilled.

One theory is that administration of mAb and TKI-directed drugs alone is limited by the underlying mechanisms of molecular oncology. The EGFR pathway is a diverse vertical and lateral signaling cascade that proceeds through multiple intracellular kinase steps before effecting gene transcription and translation.[1] The EGFR is upstream of all such cascades, which makes it a seemingly central target for blocking these downstream pathways. However, the principle of inhibiting the initiator of these pathways may actually be detrimental to the efficacy of these drugs. By nature of the complexity of these downstream pathways, there exist innumerable opportunities for the cell to bypass the EGFR. As such, many if not most cancer cells will not depend on aberrant EGFR function for their malignant phenotype. To select patients for benefit, one must determine which patients have a tumor that requires EGFR dysfunction for maintenance of growth and survival.

Conflicting Mechanisms
A second theory is derived from the observation that concurrent administration of anti-EGFR drugs with traditional cytotoxic chemotherapy may in fact be counteractive.[2,3] The molecular mechanisms of each treatment modality differ. Cytotoxics are usually cell-cycle dependent and thought to induce apoptosis through either irreparable DNA damage or inhibition of the mitotic apparatus. EGFR-directed therapies, in cancer cells that are dependent on these downstream pathways, both inhibit the cell cycle (Ras/Raf/Map kinase pathway) and reduce antiapoptotic signals
(PI3/AKT pathway). Due to their potentiation of cell-cycle arrest when given concurrently with chemotherapy, these EGFR-directed drugs may prevent the cell-cycle-dependent action of cytotoxic drugs.

From an understanding of the relationships among drug mechanisms of action, clinical efficacy, and molecular abnormalities in cancer cells follows the derivation of approaches that refine the use and thus efficacy of EGFR-directed drugs. One set of approaches is based on the biology of cells from either the cancer or the host. A retrospective analysis of tumors obtained from patients treated with combination chemotherapy and radiotherapy led to the discovery of EGFR tyrosine kinase domain activating mutations.[4] Tumors with these acquired point or deletion mutations are extremely sensitive to EGFR TKIs. This finding was translated into an ongoing clinical trial that selects patients with NSCLC harboring this mutation for first-line treatment with EGFR TKIs. Additional tumor cell characteristics that will likely enhance patient selection include EGFR gene copy number, acquired second mutations in the kinase domain and ras mutations.[5-7]

Germline patient/host factors also may impact the activity of EGFR-directed therapies. A polymorphism in EGFR intron 1 characterized by the number of CA dinucleotide repeats seems to dictate both EGFR expression and tumor cell dependency on EGFR downstream pathways, leading to greater effectiveness of EGFR drugs in cells with a lower number of CA repeats.[8] There is also a relationship between efficacy and the effect of EGFR inhibition on host normal cells as demonstrated by the correlation between skin rash and response to EGFR inhibition.[9]

Preclinical work by Perez-Soler and investigators at Memorial Sloan-Kettering Cancer Center suggests that sequencing of cytotoxics and EGFR-directed therapies affects the efficacy of these therapies when given in combination. In vitro cell-cycle studies show that giving EGFR inhibitors after cytotoxics enhances apoptosis. Treatment with high-dose, pulsed EGFR TKIs before cytotoxics also potentiates tumor cell kill. Several clinical trials that use these sequencing approaches are ongoing.[2,3]

Conclusions
The clinical development of EGFR-directed therapies demonstrates the critical and practical importance of bidirectional translation of information between the laboratory and the clinic. Although initial studies of these agents seemed disappointing, the data obtained from patients enabled researchers to determine why their efficacy was limited. This discovery of patient and tumor cell factors that enable selection of patients who will more likely benefit from these agents is likely to be validated by ongoing clinical trials.

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Disclosures:
The author(s) 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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5. Moroni M, Veronese S, Benvenuti S, et al: Gene copy number for epidermal growth factor receptor


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[1] [http://www.physicianspractice.com/authors/michael-k-gibson-md-phd](http://www.physicianspractice.com/authors/michael-k-gibson-md-phd)