Merging Medicine with Science: The Birth of a Targeted Therapy in Cancer

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We will review the development of a new anticancer therapy which acts by blocking the EGF receptor (EGFR) protein on the surface of cancer cells. The research began in 1981 and has not ended. Participants have included scientists in universities, biotech and pharmaceutical companies, the US National Cancer Institute, the Food and Drug Administration (FDA), clinical investigators at many cancer centres, and thousands of patients.

EGFR are expressed at high levels in about 1/3 of epithelial cancers, and autocrine activation of EGFR appears to be critical for the growth of many tumours. In 1981 Dr. Gordon Sato and I hypothesised that blockade of the binding site for EGFR and TGF-alpha on EGFR with an antireceptor monoclonal antibody (mAb) might be an effective anticancer therapy by inhibiting activation of the receptor tyrosine kinase. Murine mAb 225 inhibited EGFR tyrosine kinase, and inhibited tumour cell growth in cultures and in nude mouse xenografts. C225 is the human:murine chimeric version of mAb 225, administered intravenously in clinical trials. Pharmaceutical companies have developed a number of oral, low molecular-weight inhibitors which act intracellularly on the ATP binding site of EGFR, also blocking receptor activation. These molecules differ in their specificity for the EGFR receptor and their reversibility of binding. The mechanisms of tumour inhibition by these anti-EGF receptor agents involve growth inhibition through upregulation of p27Kip1, enhancement of apoptosis, and inhibition of angiogenesis and metastasis. In addition, these agents enhance the cytotoxicity of chemotherapy and radiotherapy in experimental systems. In the case of radiation therapy, inhibition of EGFR function results in inhibition of radiation-induced DNA damage repair. In the case of mAb C225, immune mechanisms may contribute to the antitumour activity. The mechanisms which may contribute to the activity of these agents against cancer are summarised in Table 1.

Table 1. Acquired Capabilities of Cancer Cells (Hanahan and Weinberg, Cell, '00)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Increased by EGFR stimulation</th>
<th>Decreased by EGFR inhibition</th>
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<tbody>
<tr>
<td>Self-sufficiency in growth signals</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Insensitivity to antigrowth signals</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Evading apoptosis</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Limitless replicative potential</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Sustained angiogenesis</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Tissue invasion and metastasis</td>
<td>yes</td>
<td>yes</td>
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These findings in extensive preclinical studies led to clinical trials of EGFR receptor inhibitors, both as monotherapy and in combination with chemotherapy or radiotherapy. Results from Phase I and II trials involving thousands of patients are promising, and data from Phase III trials have appeared. In total, nearly a dozen different experimental molecules that act by inhibiting the EGFR receptor are in the clinic. The reported results from Phase II trials, randomised trials, and trials of combination therapy have shown response rates in the range of 0% to 25%. The most common toxicity is an acneform rash, which may identify potential responders to therapy. The oral agents, but not C225, cause diarrhoea as a dose-limiting toxicity. One oral agent, Iressa, has been approved by the FDA as monotherapy treatment for advanced, refractory non-small cell lung cancer. On February 12, 2004, the US FDA approved C225 (Cetuximab, Erbitux)5 for treatment of advanced colorectal cancer.

Many challenges remain to be addressed in the clinical application of anti-EGF therapies. Is EGF receptor signalling different in cancer cells expressing 10 receptors than in normal cells expressing 10? Why do some but not all patients with an EGF receptor-expressing cancer respond to receptor inhibitors? Are there markers that could identify responsive cancers? What are the specific mechanisms for synergism between EGFR receptor inhibitors and chemotherapeutic agents or radiation, and between EGFR receptor inhibitors combined with agents promoting apoptosis or blocking angiogenesis? Do the differences between mAbs and low molecular-weight inhibitors of EGFR translate into differences in clinical activities? These questions suggest the need for further preclinical studies, for carefully targeted clinical trials that measure molecular effects of therapy, and for ways to speed up the sequence of trials required to evaluate new therapies that may work best in combinations.

Many lessons have been learned from the experience of discovering a cancer treatment and bringing it to the clinics, a process that in this case took 22 years. Some of these include:

- When new therapies targeting genetic or molecular abnormalities in cancer cells are discovered, research-seeking markers to identify patients likely to respond should be initiated early, in parallel with late preclinical studies and initial clinical trials.
- Phase I trials must be designed to establish the optimal biological dose in addition to the maximum tolerated dose – necessitating well designed and adequately funded pharmacodynamic studies of tumour tissue with molecular assays and PET imaging.
- Agents targeting a single gene or protein are not likely to produce high response rates in cancers which have multiple genetic abnormalities, so combination therapy must be encouraged early in the approvals process.
- Universities must place greater emphasis on nurturing, incentivising and promoting faculty with strong skills and long experience in clinical trials research. They require protected time for planning and carrying out experiments, similar to laboratory researchers.
- The off-label use of anticancer agents alone and in combinations, in the setting of vetted clinical trials, should be encouraged and funded.
- Improved clinical trial design can move through the sequence of Phase I-III clinical trials more rapidly by building on previous data.
- FDA regulations should encourage innovation in the drug approval process while protecting the public. This will require more flexibility and openness to expert consultation early in the process of clinical trial design and approval.

REFERENCES