Novel Compounds in the Therapy of Breast Cancer: Opportunities for Integration with Docetaxel

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ABSTRACT

Increasingly, novel agents are being developed specifically at inhibition of growth factor receptors and events within the signal transduction pathway. These agents include the epidermal growth factor tyrosine kinase inhibitors, the farnesyl transferase inhibitors, and bcl-2 antisense oligonucleotides. Along with these new approaches to molecular targeting, it will be necessary to develop new study designs for drug evaluation. Target validation in both normal surrogate tissues and tumor tissue becomes increasingly relevant in early clinical trials. Furthermore, antitumor efficacy may no longer correlate with normal hematological or nonhematological toxicity, and it may be more appropriate in phase I trials to identify the maximum target inhibition dose rather than the maximum tolerated dose. Moreover, measures of cytoreduction, such as complete and partial response, may be less relevant than disease stabilization for some of these novel agents which have limited cytotoxic effects and would be considered cytostatic agents. Assessment of single-agent activity and the future role in conjunction with cytostatic agents represents the single most important challenge facing the clinical development of these molecular targeted therapies. The Oncologist 2001;6(suppl 3):40-44

INTRODUCTION

Several major new classes of agent are now emerging from phase I/II study. The epidermal growth factor receptor tyrosine kinase inhibitors are the focus of considerable current interest based on the critical role members of the HER family have in cellular proliferation in some tumors. Although, enthusiasm for the farnesyl transferase inhibitors has waxed and waned over the past several years, single-agent antitumor activity has now been observed and has directed development in tumors where inhibition of signal transduction appears to yield antitumor activity, such as breast cancer. Finally, antisense oligonucleotides directed to the bcl-2 gene also may hold promise.

AGENTS TARGETED AT THE EPIDERMAL GROWTH FACTOR RECEPTOR

The epidermal growth factor receptor (EGFR) is an important target in cancer therapy [1-4]. The EGFR family includes HER-1 (EGFR-1), HER-2, HER-3, and HER-4, and these are expressed in combination in most epithelial-based receptor cells. Activation of these receptors by ligand binding or overexpression leads to phosphorylation of the cytoplasmic ATP binding domain and activates the mitogen-activated proliferation kinase pathway of the signal transduction pathways. From this family of receptors, HER-2 neu has been the prototype in breast cancer [5-8]. Overexpression of HER-2 by gene amplification in breast cancer tumors leads to constitutively activated tyrosine kinase activity, increased cellular proliferation, and a poor clinical outcome. EGFR-1 and the role of cellular proliferation represents an emerging target in many disorders [9].

Members of the EGFR family can be targeted either through the use of specific antibodies, Herceptin being the first such agent, or through the use of more recently developed small molecules which inhibit tyrosine kinase (TK) [10-17]. The humanized monoclonal antibody IMC-C225 directed at EGFR-1 is currently further along in development. This high-affinity antibody is directed to the cysteine-rich domains of the EGFR where it blocks ligand-induced TK activity, inhibiting activation of the MAP kinase pathway [18-21]. This results in decreased cell cycle traverse and potentiation of apoptosis. In addition, inhibition of EGFR may also

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inhibit the angiogenic growth factors and potentiate effects of both radiation and chemotherapy [22].

The development of C225, however, has to some extent been eclipsed by EGFR tyrosine kinase inhibitors, which are directed toward the tyrosine kinase function of the EGFr receptor. EGFR TK inhibitors bind to the ATP binding site on the internal membrane of EGFR. The agents undergoing clinical development include the reversible inhibitors of ZD 1839 (which are highly specific for EGFR-1) and OSI 358,774 [23, 24]. The latter agent is now in phase II study, while ZD 1839 has moved directly to phase III trial in non-small-cell lung cancer.

A second generation of EGFR TK inhibitors has been designed to have a broader spectrum of antitumor activity and to target a wider range of the erbB family. Thus, they inhibit not only EGFR-1 but also HER-2 neu, for example. Of these irreversible inhibitors, CI-1033 (a pan-erbB inhibitor) is now completing phase I evaluation, and EKB 569 (which inhibits both erbB 1 and 2) has recently entered phase I study [25, 26]. If these agents prove fully effective and are developed, they may supplant the use of Herceptin.

Both tumor and normal surrogate tissue have been obtained to validate target inhibition of these agents. Preliminary evidence suggests that EGFR phosphorylation can be effectively inhibited in tissue specimens at clinically achievable doses [27].

**Farnesyl Transferase Inhibitors**

The cascade of signal transduction events that follows activation of the growth factor receptor offers a host of potential targets for intervention. One target of particular current interest is ras and its modification [28]. A compulsory step in ras protein activation includes the addition of hydrophobic moieties so that it can associate with the internal membrane of the cell [29, 30]. The rate-limiting step in this process is the activity of farnesyl transferase. If this process is inhibited, ras can no longer associate with the membrane [31-33]. Inhibiting ras protein action, in turn, blocks a number of signal transduction pathways [34-36].

Several farnesyl transferase inhibitors (FTIs) are in clinical development. They include the orally bioavailable agents R115777 and SCH 66336 and the oral and i.v. agent BMS 214662 [37-39]. The earlier agent, L778123, is no longer in clinical studies.

Although such agents were initially synthesized to specifically target ras, particularly in malignancies in which ras mutations are prominent, they also inhibit proliferation of cell lines such as MCF-7 which do not have ras mutations. These results suggest that FTIs may have a greater spectrum of antiproliferation effect.

Furthermore, in xenograft models, the FT inhibitor R115777, inhibits tumor growth in cell lines which express wild-type rather than mutated ras [40].

The FTI R115777 also has clinically important single-agent antitumor activity in breast cancer. In a recently reported phase II study, patients with advanced metastatic breast cancer who were refractory to chemotherapy or hormone therapy were treated with R115777 [41]. Although certain patients experienced neutropenia and thrombocytopenia at 400 mg p.o. b.i.d. dose, subsequent treatment with 300 mg b.i.d. was tolerable and was the phase II dose for most of the patients treated. Three patients (12%) had partial responses and a further nine (35%) manifested stable disease at 3 months. Although the response rate seen may not appear impressive at initial inspection, by analogy with the development of Herceptin, it should be possible to determine the characteristics of responding patients and appropriately direct therapy to those patients who may respond. The FTIs may block the downstream pathway of Herceptin and represent an alternative therapeutic strategy in breast cancer. Furthermore, the FTIs may prove to have a broader spectrum of activity against targets in the signal transduction pathway. Combinations of agents that target HER family tyrosine kinases and downstream signal transduction elements may in the future overcome resistance to Herceptin.

Evidence to date suggests that the FTIs may act in synergy with the taxanes but not with other classes of cytotoxic drugs [42]. In two phase I studies about to recruit patients, R115777 will be combined with either paclitaxel or docetaxel. An NCI-sponsored study of R115777 with Herceptin is actively accruing patients, and the natural development will include a taxane, FTI, and Herceptin.

The agents considered so far have acted at a variety of points within the growth factor receptor ras MAP kinase pathway (Fig. 1). In addition, agents now in phase I development target the PI 3 kinase pathway, and hence represent another element in the molecular processes that underlie proliferation. One can envision specific targeting of tumors based on the specific signal transduction pathway used for proliferation.

**Antisense Oligonucleotides**

Reducing cell proliferation is one element in the therapy of cancer. Predisposing tumor cells to undergo apoptosis is an intervention intended to tip the other side of the balance in a favorable direction. In this process, the bcl gene is a clear target. This gene is overexpressed in several malignancies, including prostate, breast, colon carcinomas, melanoma, and some lymphomas [43-45]. Overexpression may also confer resistance to cytotoxic chemotherapy and irradiation. Downregulation of bcl-2 protein expression may therefore enhance the efficacy of antitumor agents.
Antisense oligonucleotides are small strands of nucleotides complementary to certain portions of mRNA which degrade mRNA in a sequence-specific manner [46, 47]. G1319, a drug under development which targets bcl-2, hybridizes with the first six codons of bcl-2 mRNA [48, 49]. This leads to ribonuclease digestion of the mRNA and subsequent downregulation of the protein. In certain models, this is sufficient to lead to apoptosis; in other models, bcl-2 downregulation enhances the antitumor effect of several chemotherapy agents (Fig. 2) [50-53].

Based on preclinical models, Miyake et al. and others have demonstrated that downregulation of bcl-2 with G3139 acts synergistically with docetaxel, enhancing tumor cell kill [54]. Given these data, Chen et al. have embarked on a clinical investigation of weekly docetaxel in combination with G3139 in patients with breast cancer. The antisense oligonucleotide is also being studied in San Antonio in conjunction with docetaxel administered every 3 weeks.

**DISCUSSION**

It is now recognized that agents such as those discussed above have both direct effects on a molecular target and indirect effects through inhibition of downstream events, including those involved in signal transduction.

In an attempt to more thoroughly evaluate the effects of agents directed to molecular targets, surrogate measures of biological effects are increasingly being incorporated into phase I studies alongside pharmacological parameters. The importance of these correlative studies is exemplified by the absence of conventional antitumor activity expected with antiproliferative and cytostatic agents.

Increasingly, traditional phase I studies using dose escalation to maximum tolerated dose may no longer be considered appropriate with these agents. More relevant would be studies in which there is escalation to a maximum target-inhibiting dose or a biologically relevant dose.

With conventional cytotoxic agents, increasing efficacy against the tumor target has been so closely correlated with increasing toxicity that the latter has prevented achievement of the optimal antitumor dose. With the novel agents, it may be possible to achieve antitumor activity at doses far lower than would cause significant toxicity (Fig. 3). If this proves to be true, the means used for assessing new anticancer agents will have to be fundamentally reassessed with study designs incorporating both toxicity assessment and target validation.

While demonstration of tumor regression is still an essential step in the development of traditional cytotoxic agents, this may no longer be appropriate for novel agents. Given their reduced toxicity, demonstration that they delay tumor growth may be sufficient to justify their clinical trial, particularly in combination (Fig. 4). If this is seen to be the case, there will be a move from the classical measures of cytocidal such as complete and partial response to time to progression and time to treatment failure, as appropriate measures of an agent’s utility prior to evaluating the gold standard endpoint—survival (Fig. 5).
**Figure 4. Patterns of antitumor effects.**

- **Tumor regression**
  - Control
  - Increasing doses of new agent

- **Tumor growth delay**
  - Control
  - Increasing doses of new agent

**Figure 5. Beyond phase I: screening for efficacy.**

- **CR** = complete response
- **PR** = partial response
- **MR** = moderate response

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