8 Combinations of Cytotoxic Drugs, Ionizing Radiation and EGFR Inhibitors

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8.1 The EGFR (ErbB) Family of Receptors in Cancer

Growth factors and their receptors play a key role in the development and progression of human cancers. They are overexpressed or aberrantly expressed in many cancers, which results in unregulated cell signalling, dysregulation of growth, tumour initiation or promotion, and invasion and metastasis, thus contributing to at least four of the six hallmarks of cancer (Hanahan and Weinberg 2000).

Within the growth factor receptors, the ErbB family of receptor tyrosine kinases and related plasma membrane receptors has been identified as critical components facilitating autocrine growth regulation that are typically the result of coordinated co-expression of growth factors and their receptors (Weinberg 1989; Baselga and Mendelsohn 1994). Although the plasma membrane components share important similarities as 170- to 200-kD transmembrane glycoproteins, each ErbB species carries a specific function within the ErbB-receptor Tyr kinase response network (Riese and Stern 1998). ErbB 1 (EGFR) and ErbB 4 are complete receptors with growth factor binding sites in the extracellular NH2-portion and a Tyr kinase domain in the cytoplasmic COOH-terminal portion of the molecule. ErbB 2 represents a constitutively active receptor without a ligand binding domain, and ErbB3 shares ligand specificities with ErbB4 but lacks Tyr kinase activity; therefore, ErbB 2 and ErbB 3 represent important modulators of cellular response to growth factors through heterodimerisation with ErbB 1 and ErbB 4 (Riese and Stern 1998; Earp et al. 1995).

These different properties of ErbB receptor tyrosine kinases determine the nature of their interactions with defined homo- and heterodimerisation hierarchies and result in receptor activation. The ErbB receptors mediate their proliferative signals through a major cytoprotective signalling pathway involving the adapter proteins (i.e. GrB2 and SHC), GTP exchange factors, such as SOS, phospholipase Cγ (PLCγ), Ras, protein kinase C (PKC), Raf, MAPK and PI-3-kinase-dependent pathways. These signalling pathways directly or indirectly affect cell-cycle control and transcription regulation initiating the biosynthetic machinery and cell proliferation (Schmidt-Ullrich et al. 1999).

8.1.1 EGFR

All cells of epithelial origin as well as many cells from mesenchymal derivation express the EGFR. A primary function of the EGFR revolves around its capacity to influence cellular growth, proliferation and differentiation. In recent years, many reports have confirmed an overexpression of EGFR in epi-

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thelial tumours. As is the case with other growth factor receptors, increased EGFR activation can result from higher levels of ligand (such as EGF), EGFR gene amplification, increased transcription or mutations that cause unregulated receptor signalling. A correlation between EGFR overexpression and disease stage, disease progression, patient survival and response to therapy has been put forth for a variety of the most common human malignancies (Wells 2000). Although this correlation between EGFR overexpression and poor clinical outcome appears convincing, a direct cause and effect relationship has yet to be firmly established. It is certainly possible that the specific reliance of a particular cell type or tissue on the EGFR pathway for growth is more important than the arithmetic quantification of EGFR.

8.1.2 EGFR Variations

Overexpression of EGFR is sometimes associated with the expression of mutated species. One mutant EGFR, named EGFRvIII, lacks a portion of the extracellular ligand-binding domain, leading to a constantly active tyrosine kinase (Huang et al. 1997). EGFRvIII is not found in normal tissues but is expressed on the cell membrane in certain tumours including gliomas, prostate, breast, non-small cell lung, colorectal and ovarian cancers (Moscatello et al. 1995). Mutations of the EGFR kinase domain have also been reported, and recent studies indicate that its frequency is rare in most types of human cancer apart from that of lung adenocarcinoma (Sihto et al. 2005). Studies of a large number of lung tumour patients identified a frequency of 24% for EGFR mutations in the tyrosine kinase domain (exons 18–21) with a higher incidence for female, young, non-smoking patients. Importantly, these mutations seem to identify distinct subsets of lung cancer patients with an increased response to an EGFR-inhibiting drug called gefitinib (Pao et al. 2004).

8.2 EGFR and Treatment Resistance

Alterations in chemosensitivity have been noted in preclinical studies of EGFR-overexpressing tumour cell lines. Indeed, higher levels of expression of drug-resistance-related proteins, such as topoisomerase II and p-glycoprotein, are found in untreated EGFR-positive renal tumours. Ogawa et al. (1993) measured EGFR expression and cisplatin sensitivity in tumour tissues from 84 patients with lung cancer. The EGFR expression was significantly higher in tumours that were resistant to cisplatin compared with cisplatin-sensitive tumours (Ogawa et al. 1993). Similarly, patients with ovarian cancer who have EGFR-positive tumours or increased transforming growth factor (TGF)-α expression have a lower rate of response to chemotherapy with cisplatin compounds compared with patients with lower EGFR levels (Fischer-Colbrie et al. 1997). Santini et al. (1991) reported that patients with head and neck tumours in which EGFR expression levels were >100 fmol/mg protein had a lower probability of response to chemotherapy than did patients with EGFR levels <100 fmol/mg protein.

Furthermore, an association between EGFR expression and clinical radioresistance has been reported in patients with cancer. Ang et al. (2004) and Giralt et al. (2002) reported a correlation between EGFR overexpression and response to radiotherapy in human head and neck cancers or rectal cancer, respectively. The EGFR expression was a significant and independent prognostic indicator for overall survival and recurrence-free survival after radiation therapy in patients with astrocytic gliomas (Zhu et al. 1996). Pillai et al. (1998) noted that patients who had residual or recurrent disease after radiotherapy for cervical cancer had more EGFR expression than those patients who were disease-free. Other authors found an inverse correlation between EGFR expression and radiocurability in murine carcinomas (Akimoto et al. 1999). Treatment of EGF protected cells against radiation in culture, whereas treatment with an antibody against EGFR induced radiosensitisation (Balaban et al. 1996). While preclinical studies indicate that EGFR inhibition can sensitise many tumour cells to ionizing radiation, in vitro sensitisation with cell lines may not reflect the prognostic implications of EGFR overexpression in vivo.

Together, the currently available data suggest that higher levels of EGFR may be associated with chemo- and/or radioresistance in some tumours. These findings therefore stimulated the research of targeted modulation of EGFR function as a new therapeutic strategy; however, the current data are insufficient to suggest using EGFR expression as a predictor of response to chemo- and/ or radiotherapy in general. It is probably more valuable to con-