Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: Evolving Role in the Treatment of Solid Tumors

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Since the 1980s, the search for new anticancer therapies has benefited from advances in the understanding of tumor biology and the genetics of cancer. A variety of agents has been discovered (e.g., targeted therapies) that stop tumor growth by inhibiting specific molecular targets in tumors. These target molecules are essential to the growth and progression of tumors but are not needed in normal tissues (Kelloff et al., 1996; Raymond, Faivre, & Armand, 2000). This is in contrast to cytotoxic chemotherapy agents that do not discriminate between killing proliferating tumor cells and normal cells and may lead to severe or debilitating drug-related toxicities. The goal for targeted therapies is to provide antitumor benefits with better tolerability.

The epidermal growth factor receptor tyrosine kinase (EGFR-TK) is one key target molecule in tumor cells that is responsible for activating multiple downstream signaling pathways governing tumor growth. Clinical trials of targeted EGFR-TK inhibitors (EGFR-TKIs) have demonstrated benefits in patients with advanced solid tumors and have been associated with unique clinical features and safety profiles compared with conventional cytotoxic therapies. Molecular targeted therapies, such as EGFR-TKIs, may provide important treatment options for patients with advanced solid tumors whose disease has progressed while receiving chemotherapy or for patients who cannot tolerate the toxicity associated with chemotherapy. Strategies for incorporating EGFR-TKIs into treatment plans for patients with solid malignancies are evolving, and their optimal use represents an active area of clinical research.

Targeting Epidermal Growth Factor Receptors

EGFR-TK plays a pivotal role in the development of many of the most common solid tumors (Dy & Adjei, 2002; Prenzel, Fischer, Streit, Hart, & Ulrich, 2001; Raymond et al., 2000). EGFR, also known as ErbB1 or HER1, is present in most cell types, with the exception of hematopoietic cells. Under normal circumstances, EGFR-TK signaling is controlled strictly. In tumor cells, however, normal regulations that limit EGFR-TK enzyme activity and the subsequent transduction of growth signals are lost. A variety of tumor cell responses results from aberrantly activated EGFR-TK, including stimulation of cell growth, promotion of cell motility, alteration of adhesion and invasiveness, prolongation of cell survival, and stimulation of angiogenesis (Herbst & Shin, 2001; Raymond et al., 2000).