INTEGRATION OF TARGETED ANTICANCER AGENTS WITH STANDARD CHEMOTHERAPY

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Targeted therapeutics represent a potential for great improvements in survival from non-small cell lung cancer (NSCLC), one of the most common and most lethal malignancies. The main categories of targeted therapies for NSCLC include receptor-targeted therapy, signal transduction or cell-cycle inhibitors and angiogenesis inhibitors. These new agents are less toxic, easier to administer, and may lead to enhanced safety and survival for patients with advanced NSCLC. Targeted therapies are now in different phases of clinical testing and have shown encouraging activity as single agents or in combination with chemotherapy as well as radiation therapy (1). In addition to NSCLC, colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death. For nearly 50 years, 5-FU dominated the chemotherapy regimens for patients with metastatic CRC (mCRC). In the past 10 years, development of irinotecan, oxaliplatin and capecitabine improved mCRC treatment. More recently, monoclonal antibodies such as bevacizumab, cetuximab, and panitumumab have become available for use in combination with cytotoxic agents. The addition of these targeted agents to the mCRC treatment has expanded the therapeutic options and improved treatment outcomes. The prospect of mCRC treatment is ever promising as more targeted agents such as vatalanib are being introduced (2). Finally, the interaction between ZD6474, an inhibitor of tyrosine kinase of vascular endothelial growth factor receptor-2 (VEGFR-2) and epidermal growth factor receptor (EGFR), gemcitabine, and ionizing radiation in human pancreatic cancer cells demonstrated that, in vitro, ZD6474 dose dependently inhibited cell growth, induced apoptosis, and synergistically enhanced the cytotoxic activity of gemcitabine and ionizing radiation. Moreover, ZD6474 inhibited phosphorylation of EGFR and Akt and triggered cell apoptosis. In vivo, ZD6474 showed significant antitumor activity alone and in combination with radiotherapy and gemcitabine, and the combination of all three modalities enhanced MIA PaCA-2 tumor growth inhibition compared with gemcitabine alone (3). In conclusion, rationally-designed combination regimens of cytotoxic drugs and targeted agents are being designed based upon a better understanding of pharmacokinetics and pharmacodynamics and hold the promise to open up a new era of combination chemotherapy.

1) Blumenschein G.R. Jr and Herbst R.S. (2003) Clin. Lung Cancer 4:217-23.
2) Saif MW, Kang SP, Chu E. (2006) Oncology 20(14 Suppl 10):11-9.
3) Bianco C., Giovannetti E., Ciardiello F., et al. (2006) Clin. Cancer Res. 12:7099-107.