

PREFACE

The concept of combining chemotherapeutic agents to increase cytotoxic efficacy has evolved greatly over the past several years. In the past, the rationale for combination chemotherapy centered on attacking different biochemical targets, overcoming drug resistance in heterogeneous tumors, and increasing the dose-density of combination chemotherapy to take advantage of tumor growth kinetics. The overall goal was to improve clinical efficacy with acceptable clinical toxicity. We are now moving to a new generation of drug therapies. An understanding of the molecular basis of tumor cell growth and differentiation has resulted in the identification of new targets for cancer therapy. These targets range from proteins that regulate the cell cycle to cell-surface receptors that mediate signal transduction events. However, despite promising preclinical activity as single agents, early clinical trials with these drugs have proven disappointing, with rare clinical responses. This may be explained by the fact that these agents are not classic cytotoxic drugs. Instead, the interruption of intracellular signals is capable of inducing growth arrest with minimal cell death. Recent studies indicate that these new agents are potent potentiators of chemotherapy-induced apoptosis. It is now apparent that the future clinical development of these molecularly targeted therapies will depend on the modulation of molecular events that will enhance the efficacy of our classic cytotoxic drugs. Therefore, as these drugs become part of our clinical programs, it will be essential to understand how to combine them with traditional chemotherapy. For example, it is now apparent that the sequence of administration of cyclin-dependent kinase inhibitors relative to chemotherapy can either enhance or antagonize the chemotherapeutic effect. These sequence-dependent effects can be explained by cell cycle perturbations, or by pharmacodynamic interactions between the agents in combination. An understanding of these drug interactions will be critical for the successful introduction of these new agents into traditional clinical use. Thus, it does not appear that we will be abandoning traditional cytotoxic agents for the new molecularly based approach to oncology. Rather, current studies indicate that chemotherapy and cytotoxic agents will continue to serve as a foundation upon which the next generation of new small molecules will be added as modulators and potentiators. In *Combination Chemotherapy: Modulators and Potentiators*, we focus on novel drug combinations with new agents that hold the most promise for the future of medical oncology. They run the gamut of targeted therapies against cell surface receptors (EGF-R and HER2), the cell cycle (the CDKs), signal transduction events (PKC and NF- κ B), apoptosis (bcl-2), as well

as novel targeted therapies in ovarian cancer, hematologic diseases, and breast cancer. The emphasis is on new translational approaches that are being moved from the laboratory bench top to the patient's bedside for the future treatments in cancer therapy.

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