Introduction

Cancer is a leading cause of death in adults and children, with over five million new cases diagnosed in more developed countries each year and more than twice that number worldwide[1]. Multi-modality treatment, comprising chemotherapy, surgery, radiation and supportive care, has contributed to major advances in the cure of many human cancers (*e.g.*, childhood acute lymphoblastic leukemia has an 80% cure rate today compared to less than 10% in the 1960s). Furthermore, improved diagnostics and screening modalities have contributed to the early diagnosis of many cancers, often at a stage when it is the most curable (*e.g.*, mammography and breast cancer, colonoscopy and colorectal cancer). Encouragingly, enhanced preventive measures have lowered the frequency of some cancers, exemplified by smoking cessation and the reduction of lung cancer. Despite this impressive progress, much remains to be done, as cancer death rates for all human cancers combined exceed 50%, even within more developed countries.

Major advances in elucidating the molecular basis of many cancers have fueled a burgeoning effort to develop more molecularly targeted treatments. These include the tyrosine kinase inhibitor imatinib mesylate (Gleevec™), which inhibits tyrosine kinase overexpression in human leukemia cells with chromosomal translocations leading to *bcr-abl* gene fusion. Despite the enormous potential of molecularly targeted therapeutic agents, it is clear that single-agent therapy is unlikely to be curative in most human cancers, evidenced most recently by the emergence of resistance to imatinib mesylate secondary to *bcr-abl* gene mutations or amplification. Furthermore, it is likely that cytotoxic chemotherapy will continue to be an important treatment modality to reduce the initial disease burden, to a level that is more amenable to molecularly targeted therapies.

[1] GLOBO Scan 2000, http://www-dep.iarc.fr/globocan/globocan.html

Because cytotoxic chemotherapy affects both normal and malignant cells, and these agents typically have very narrow "therapeutic indices" (the difference between systemic exposure required for therapeutic efficacy versus host-toxicity), interindividual differences in the pharmacokinetics of these medications can influence patient outcomes by either enhancing toxicity, reducing efficacy, or both. Therefore, it is typically a "balancing act" to select the dose of cancer chemotherapy that will produce the desired anticancer effects without undue toxicity, often in the context of treatment with multiple cytotoxic agents.

During the 20 years from 1980 to 1999, studies of the pharmacokinetics and pharmacodynamics of cancer chemotherapy have revealed important new insights into the nature of interindividual differences in the disposition of these medications and its influence on patient outcomes (toxicity or efficacy). These human pharmacokinetic and pharmacodynamic studies have documented that differences in the absorption, distribution, metabolism and/or elimination of cancer chemotherapy can have a significant influence on patient response and treatment outcome, by either avoiding toxicity, enhancing efficacy, or both.

The publications included in this compendium were selected because they have advanced the field of cancer pharmacotherapy by extending beyond traditional clinical pharmacokinetic studies of anticancer agents, to elucidate either a) the pharmacodynamics (*i.e.*, concentration-effect relationship); b) the intracellular disposition in the target tissue of patients (*i.e.*, cancer cells); or c) the pharmacogenetics of cancer chemotherapy (*i.e.*, the inherited basis for interpatient differences). Papers 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 14, 16, 17, 19, and 20 (see the index page) focus on the clinical pharmacodynamics of cancer chemotherapy, defining relationships between systemic exposure and either drug toxicity (1, 3, 7, 10, 12, 16, 17) or anticancer effects (2, 3, 4, 8, 11, 14, 19, 20). Papers 5, 8, 9, 18, 21 and 22 focus on the pharmacogenetics of cancer chemotherapy, in some cases defining the relationship between these inherited differences in drug disposition and the clinical toxicity or treatment efficacy of cancer chemotherapy. Two papers (13, 15) were included because they extended pharmacokinetic studies to the target tissue in patients (*i.e.*, primary cancer cells).

Criteria used in the final selection of papers included their novelty, their primacy in terms of major findings, and the total number of citations of the publication by subsequent investigators (in brackets in the index page). The papers included are intended to be representative of important advances

made in the 20-year period from 1980 to 1999, and not a comprehensive compilation of all important work in this field. It is almost certain that a number of important papers have not been included, either due to imperfections in the searching process or space limitations; the editors and publisher apologize to those whose important work has not been included. We applaud all those who have contributed to the advance of cancer treatment by elucidating the pharmacodynamics of cancer chemotherapy and applying this new knowledge to optimize treatment of patients.

William E. Evans and Mary V. Relling
Department of Pharmaceutical Sciences St. Jude Children's Research Hospital, Memphis USA
May, 2003