Pharmacologic Treatment of Cancer: New Developments

In this issue of Cancer Control, five reviews address the current state of the art for the pharmacologic treatment of cancer. For centuries, surgery was considered the only curative treatment for cancer. Likewise, radiation therapy offered some patients a possible cure for cancers that were localized. However, once the disease spread from its original site of origin, the patient was deemed inoperable and therefore incurable. This self-fulfilling prophecy remained true until the development of systemic therapy that addressed not only localized disease, but also disease that had spread to distant sites. Cytotoxic drugs represent the most commonly used treatment for cancers that have metastasized, although hormones can have a major impact in diseases such as breast and prostate cancer.

The first drug used for cancer treatment was a derivative of mustard gas. In 1948, Farber and associates reported on the use of folate antagonists for the treatment of childhood leukemia. Since that time, over 100 pharmacologic agents have been introduced for the treatment of cancer. Successes in the treatment of systemic cancer with these agents have improved dramatically over the last two decades. Combining agents with different mechanisms of action and non-overlapping toxicities is now considered the most acceptable approach to the eradication of disseminated cancers. The most effective setting for the use of pharmacologic agents may be in the adjuvant setting following primary treatment with surgery or radiation therapy when the tumor is in a minimal residual disease state. However, for certain tumors, such as testicular cancer or malignant lymphoma, combination chemotherapy is potentially curative even in the face of widely metastatic disease. This progress is graphically underscored by the recent successful treatment and recovery of cyclist Lance Armstrong, the winner of the 1999 Tour de France who was diagnosed with stage III testicular cancer. However, despite such successes, numerous challenges exist for the clinician in treating patients with metastatic cancer.

The chief obstacle to curing a patient with cancer is the development of recurrent disease that is resistant to currently available agents. Considerable effort has been made to identify cellular mechanisms that confer drug resistance in cancer cells in order to develop approaches to overcome or prevent drug resistance. Indeed, important mechanisms have been identified in cancer cells, and clinical studies are now in progress to improve outcome by overcoming particular mechanisms of drug resistance. Perhaps the most important observation made to date is that multiple mechanisms of cellular drug resistance exist and these mechanisms are non-exclusive. In other words, attempting to overcome a single mechanism of drug resistance in cancer patients is not likely to produce a cure due to the complexity of the clinical drug resistant phenotype. Because of the multifactorial nature of drug resistance, it will be important to develop novel pharmacologic agents that do not participate in the most common mechanisms identified to date.

In this issue of Cancer Control, novel pharmacologic agents are reviewed that may ultimately improve clinical outcome of cancer patients. In the review by Dr Bowman and colleagues, a new target for drug discovery has recently been identified that may be relevant for both hematologic and solid tumors. This review discusses recent progress in understanding how aberrant activation of the STAT signaling pathways may result in malignant progression. Evidence provided in this review indicates that one mechanism by which STAT activation may contribute to tumor progression involves the prevention of programmed cell death, or apoptosis, which in turn confers a survival advantage for the tumor and may contribute to the development of chemotherapy resistance. These advances identify STATs as a novel molecular target for drug development in tumors harboring aberrant STAT activation.

A second approach to new drug development for disseminated cancers is reviewed by Dr Brem. Developing drugs that attack or prevent the formation of tumor blood vessels may prove to be effective in the treatment of cancers that are resistant to traditional chemotherapy. Exciting new agents that inhibit tumor angiogenesis are now currently undergoing clinical trials.

In a review by Dr Lush and colleagues, three new classifications of agents are discussed including antiangiogenic agents, agents that inhibit matrix metalloproteinases, and agents that modulate cyclin-dependent kinases. The development of agents targeting novel molecular targets engenders an appropriate optimism for the treatment of patients with metastatic cancer.

Finally, two reviews address the important considerations of quality of life and tolerance to chemotherapy. Drs Balducci and Beghé discuss the treatment of the older cancer patient and how chemotherapy may need to be "tailor-made" for the older patient, with consideration given to comorbid illnesses or age-related deterioration of organ function that may reduce tolerance to treatment. This issue is particularly important, given the fact that cancer is particularly prevalent in the elderly and that the median age of Western populations is increasing. Drs Jacobsen and Weitzner discuss the important issue of quality of life and the methodologic challenges that need to be addressed in evaluating palliative endpoints in cancer clinical trials. The issue of quality of life is just as important as quantity of life, and the development of new pharmacologic agents that improve the quality of life for patients with advanced disease are highly valued. Accordingly, it is important to develop methods to accurately assess these agents before they reach wide use and become incorporated as standard care.

These are exciting times for new drug development and the treatment of cancer. We are undergoing an information explosion regarding the cellular biology and unique characteristics of cancer cells compared with normal cells. This new information is being translated into clinical use by identifying new drug targets that may not only prevent cancer progression, but also spare the patient from undue toxicity. Cautious optimism should prevail for all investigators involved in translating these exciting new biological findings into new pharmacologic agents for the treatment of cancer.

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References