Crossing the Cancer Cell Membrane to Improve Clinical Outcomes

ERIC K. ROWINSKY

Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, Texas, USA

Key Words. Signal transduction · Recombinant human erythropoietin · Ras protein · Farnesyl transferase inhibitors · Multiple myeloma · Thalidomide

INTRODUCTION

Over the past 30 years, there has been a steady increase in the number of malignancies that can be treated with curative rather than palliative intent. A primary reason for this is the exhaustive research efforts under way to better understand the biology of malignant cells, as well as advances in both chemistry and biotechnology, all of which are leading to an age of more rational therapeutics for neoplasms. These new and emerging therapies may improve the quality of life of cancer patients, reduce the number and length of hospital stays, and potentially improve survival. In addition, supportive therapies can ameliorate many of the more serious adverse consequences (e.g., anemia) of cancer and its treatment, as well as potentially have a positive effect on patient outcomes.

Many of the advances contributing to improvements in cancer therapy have resulted from the development of therapeutics that target specific tumor cell populations or that interact with key components of signaling pathways that mediate cellular growth and differentiation, which are aberrant and/or overexpressed in cancer cells [1]. Additional areas of investigation potentially valuable to rational therapeutic development involve those aspects that essentially define a cell as malignant or neoplastic, including evasion of apoptosis, sustained angiogenesis, tissue invasion and metastasis, and immune tolerance.

This supplement updates and expands upon presentations made at a symposium entitled Penetrating Insights: Crossing the Cancer Cell Membrane to Improve Clinical Outcomes, held on December 6, 2002, preceding the 44th Annual Meeting of the American Society of Hematology in Philadelphia, PA. The objectives of this supplement are to provide clinicians and researchers with recent insights into signaling pathways and selected receptor systems that are the focus of cutting-edge cancer therapy research, with a focus on improving outcomes for patients with acute leukemia, lymphoma, multiple myeloma, and selected solid tumors.

The first article in this supplement, by Dr. Eric Rowinsky (Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, TX), describes the basic aspects of signal transduction, a communication method used by regulatory molecules to mediate essential cell processes of growth, differentiation, and survival [2]. Elements of the signal transduction process interact biochemically through related networks, and anomalies in these elements may lead to increased proliferative potential, sustained angiogenesis, tissue invasion and metastasis, and apoptosis inhibition [3-6]. A number of compounds in development that target aberrant signal transduction elements, including those in the ErbB family of tyrosine kinase receptors and mammalian target of rapamycin (mTOR) [7-11], are identified and described. Commercially available signal-transduction-targeting therapeutics include trastuzumab, a monoclonal antibody against the ErbB-2 receptor for the treatment of metastatic breast cancer overexpressing the ErbB-2 (HER-2) receptor [11-13], and gefitinib, an inhibitor of the ErbB-1 receptor tyrosine kinase for the treatment of patients with non-small cell lung cancer [14, 15]. Also discussed are the needs for new clinical trial designs and evaluation end points as well as the prospective patient profiling that will most effectively assess the value of signal transduction inhibitors, largely because preclinical and early clinical investigations suggest that their predominant beneficial effects are growth inhibitory in nature.
In the realm of supportive therapy, Dr. Mitchell Weiss (University of Pennsylvania School of Medicine, Philadelphia, PA) reviews the mechanism of action of erythropoietin (EPO) in erythropoiesis and its related effects in cancer patients [16]. In addition, Dr. Weiss details the evidence for EPO actions in addition to erythropoiesis, as well as potential therapeutic uses for recombinant human erythropoietin (rHuEPO, epoetin alfa) both in and beyond anemia treatment. In addition to the proven benefit of epoetin alfa in the management of anemia in patients with cancer receiving chemotherapy, the cytokine also produces improvements in quality of life that are associated with increases in hemoglobin levels [17-21]. Preclinical models of neurologic diseases have allowed researchers to demonstrate that EPO confers a neuroprotective effect via inhibition of neuronal apoptosis [22-23] and may provide neuroprotection in patients with stroke [24]. Preliminary data suggest that epoetin alfa may also attenuate chemotherapy-associated cognitive dysfunction in patients with breast cancer undergoing anthracycline-based chemotherapy [25]. Dr. Weiss also discusses evidence that established pathways, as well as a novel pathway that links Janus kinase 2 and nuclear factor-kB, appear to be key to EPO signaling in the central nervous system [26].

Dr. Said Sebti (H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, FL) provides evidence for the fundamental roles that Ras proteins play in cell signal transduction pathways that regulate cell growth, differentiation, proliferation, and survival [27]. Mutations of these proteins are among the most frequently encountered genetic abnormalities in human cancers and, thus, are key to tumor development [28, 29]. The enzymatic attachment of a 15- or 20-carbon moiety to the Ras protein through farnesylation or geranylgeranylation, respectively, is required for the appropriate localization and activation of Ras [28, 30]. Dr. Sebti describes a novel, mechanism-based, targeted approach to cancer therapy development in which the catalytic enzymes, farnesyl transferase and geranylgeranyl transferase (GGT), are inhibited [30]. Farnesyl transferase inhibitors (FTIs) may prevent bipolar spindle formation, which blocks progression from prophase to metaphase, and GGT inhibitors prevent tumor growth by arresting cells in the G_1/S cell cycle phase [30]. Dr. Sebti hypothesizes that the molecular target responsible for the antitumor activity of FTIs may be mediated through the phosphoinositide-3-OH kinase/AKT2-mediated cell survival and adhesion pathways, and encourages ongoing research to identify the specific signaling pathways responsible for the clinical activity of FTI and GGT inhibitors.

In reviewing novel drug delivery methods, Dr. Mohamad Hussein (Cleveland Clinic Myeloma Research Program, Cleveland, OH) describes a novel alternative to the combination of vincristine/doxorubicin/dexamethasone (VAD) [31]. VAD is an effective treatment for multiple myeloma that produces a rapid response but is cumbersome to administer, requiring hospitalization for a 96-hour continuous infusion delivered via a central venous catheter [32-34]. Potential modifications to this combination include replacing doxorubicin with pegylated liposomal doxorubicin [35-39], decreasing the administration frequency of dexamethasone (DVd) [40, 41], and possibly adding thalidomide to the regimen (DVd-T) [42, 43]. Dr. Hussein describes the interim results of an ongoing study in patients with relapsed/refractory multiple myeloma, which suggest that DVd-T may improve the rate and quality of response over previous regimens [44]. Additional follow-up may further define the significant potential of this regimen in the management of advanced myeloma.

These reviews provide tantalizing evidence for the role of rational therapeutics in the management of a variety of cancers. Numerous questions remain regarding the mechanisms, therapeutic potentials, and toxicities of cancer agents developed following the expansion of cancer research to a more specific understanding of the basic chemical and biological elements of neoplasia. Ongoing research is likely to increase our understanding of these basic elements, which, in turn, may provide new targets for therapeutic agents. Regimens incorporating new therapeutics with standard cytotoxic agents are being, or soon will be, evaluated in clinical trials to further increase the range of cancers that can be treated with curative intent.

References


39 Hussein MA, Tonda ME, George S et al. A phase III randomized trial of Doxil®/CAELYX®, vincristine, and dexamethasone (DVd) versus vincristine, Adriamycin®; and reduced-dose dexamethasone (VAd) in the treatment of patients with newly diagnosed multiple myeloma (n-MM) [poster]. Presented at the


44 Hussein MA, Elson P, Tsoe EA et al. Doxil (D), vincristine (V), decadron (d) and thalidomide (T) (DVd-T) for relapsed/refractory multiple myeloma (RMM) [abstract]. Blood 2002;100:403a.