Second Symposium of Novel Molecular Targets for Cancer Therapy

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INTRODUCTION

For the past 30 years, the survival rate of the majority of adult patients with malignant solid tumors has not significantly increased. Conventional chemotherapeutic agents aim at the classic targets for cancer therapy: tubulin, DNA, RNA, and protein synthesis. These cytotoxic agents are “tumor-selective” only if the tumor cells proliferate faster than normal cells, which is not always true.

During the past several years, researchers have begun to realize that cancer therapy may be more effective if the proteins associated with specific pathways for cancer transformation and progression (e.g., apoptosis, angiogenesis, cell-cycle regulation, signal transduction, and invasion) are blocked [1, 2]. Such novel molecular targets include proteases, tyrosine kinases, ligands, and receptors. While blocking of these targets is cytostatic rather than cytotoxic, the blocking particularly of molecules that promote proliferation and antagonize apoptosis sensitizes tumor cells to cytotoxic therapy. Thus, a combination of molecular target inhibitors and standard cytotoxics appears to provide real tumor selectivity.

Cancer research has provided insight into the processes responsible for cancer growth and identified numerous molecular targets for cancer therapy [1, 2]. However, the procedure to approve their use in cancer therapy is lengthy. Upon selection of a target, small molecules from natural or synthetic compound libraries are screened for both modulation of the target and antitumor effect in in vitro and in vivo assays. Small molecules that score high (lead compounds) are assessed in animal models regarding pharmacokinetics and pharmacology. Following pharmacokinetic improvements, the compound is evaluated for safety and efficacy in phase I-III clinical trials. Novel designs of phase I trials with small molecules also aim to evaluate target modulation, preferably measured in tumor tissues. If trial outcomes are favorable, a New Drug Application is submitted to the Food and Drug Administration for approval to use the compound in cancer treatment.

This supplement to The Oncologist is based on the proceedings of the Second Symposium of Novel Molecular Targets for Cancer Therapy, which was held October 4-5, 2001, in Buenos Aires, Argentina. The National Institute for Dental and Craniofacial Research (NIDCR), The National Cancer Institute [both at the National Institutes of Health (NIH)], and the International Society for Translational Research sponsored the symposium. Approximately 600 oncologists and basic cancer researchers discussed novel molecular approaches in cancer therapy. This set of articles highlights recent and ongoing cancer research on various agents, including vaccines and kinase inhibitors.

The first article in the supplement, by Dr. Claudio Conti (University of Texas M.D. Anderson Cancer Center), discusses targets in angiogenesis, in particular the proangiogenic vascular endothelial growth factor (VEGF) [3]. Angiogenesis, the formation of new blood vessels, is necessary for tumor growth beyond 2 mm in diameter, as well as for invasion and metastasis [4]. Whereas hypoxia triggers angiogenesis by generating a series of angiogenic factors including VEGF [5], in
many tumors angiogenesis is induced by genetic alterations—e.g., activated H-ras induces VEGF [6]. Dr. Conti shows that angiogenesis in the mouse skin carcinogenesis model is not induced by hypoxia: VEGF expression is detected in premalignant papillomas and squamous cell carcinomas, but not in anoxic tumor areas (Conti and Franco, unpublished results). Rather, angiogenesis in this model appears to be dependent on H-ras, which is activated in papillomas [7], and the endothelial growth factor receptor. Thus, like VEGF, oncogene pathways may be targets for antiangiogenesis cancer therapy. VEGF is currently targeted in cancer patients in clinical trials using anti-VEGF antibodies, soluble VEGF receptors, or dominant-negative VEGF-receptor 1 [8-10].

Dr. Adrian Senderowicz (NIDCR, NIH) summarizes research on novel therapeutic targets in the cell cycle [11]. Most cancers have alterations in the cell-cycle pathway [12, 13], which lead to activation of cyclin-dependent kinases (CDKs) and subsequent inactivation of retinoblastoma. The small molecule flavopiridol inhibits CDKs by binding their ATP-binding pocket [14, 15]. A review of phase I clinical trials indicates that flavopiridol demonstrated antitumor activity in some patients with non-Hodgkin’s lymphoma as well as renal, prostate, colon, and gastric carcinomas [16, 17]. Phase I clinical trials employing different schedules of flavopiridol and combinations of flavopiridol and standard chemotherapeutics are ongoing [18-22]. Dr. Senderowicz also reviews data from clinical trials with the small molecule UCN-01 (7-hydroxystaurosporine), which inhibits protein kinase C, CDKs [14], and protein kinase Chk1 [23, 24]. Phase I trials of UCN-01 combined with chemotherapy in several tumor types including head and neck squamous cell carcinoma are planned.

Dr. Igor Espinoza-Delgado (National Institute on Aging, NIH) addresses the use of vaccines in cancer therapy [25]. A protective effect of the immune system against cancer growth was suggested by the observation that some human tumors regress spontaneously. The ability of the immune system to recognize tumor-associated antigens found on human malignancies and then to direct cytotoxic responses, especially via cytotoxic T lymphocytes, has been demonstrated in several preclinical models. Early human clinical trials, particularly in melanoma, have confirmed that cancer vaccines induce immune responses that are tumor-specific and, in some cases, associated with clinical responses. Dr. Espinoza-Delgado discusses various vaccination-based therapies, including peptide-based vaccines, gangliosides (GM2/BCG), cellular vaccines (dendritic cells, autologous or allogeneic tumor cells, and tumor—antigen-presenting cell [APC] hybrids), and idiotypic vaccinations. He reports that one immediate challenge is determining how to appropriately stimulate the pathways leading to effective interaction among APCs, T lymphocytes, and tumor cells, thereby avoiding the development of T-cell anergy and tolerance. Another challenge is to develop monitoring strategies to identify patients who may benefit from cancer vaccines.

The final article in the supplement, by Dr. Bruce Chabner (Massachusetts General Hospital), focuses on the future of cancer pharmacology [26]. Specifically, Dr. Chabner discusses the use of pharmacogenomics and pharmacogenetics to customize cancer therapy. Customized therapy may be used to decrease cytotoxicity in patients and/or to avoid or overcome tumor drug resistance. Tumor drug resistance may further be avoided/overcome by treating patients with combinations of standard cytotoxic agents and compounds directed at novel targets [27]. Although novel agents appear to be a promising therapeutic approach, their response is often unpredictable and, therefore, their activity and target modulation need to be investigated in a wide range of tumors. Inasmuch as clinical trials with these compounds may take several years to complete, Dr. Chabner underscores the need for development of surrogate markers that not only measure target modulation but also predict tumor response following treatment with a novel compound. Many questions remain regarding the efficacy of agents directed at novel targets. Yet, because these agents affect processes necessary for cancer transformation and progression, their use alone or in combination with standard cytotoxics is likely to lead to improved therapeutic results. Indeed, Gleevec™ (imatinib mesylate; Novartis Pharmaceuticals Corporation; East Hanover, NJ), an inhibitor of Bcr-Abl kinase and c-kit, provides an important model for this rapidly growing field.

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