Henry Wagner, Jr, MD  
Thoracic Oncology Program,

H. Lee Moffitt Cancer Center & Research Institute


The classic radiobiologic teaching of 20 years ago instructed that the direct or indirect effects of ionizing radiation on DNA were responsible for cell death. This investigation demonstrates that radiation of bovine aortic endothelial cells or cell membranes in a nuclei-free system can activate portions of a signal transduction pathway involving hydrolysis of the membrane lipid sphingomyelin to yield ceramide, which activates a downstream serine-threonine protein kinase. This radiation-activated pathway leading to apoptosis was blocked by activation of protein kinase C, suggesting points for possible pharmacologic modulation of radiosensitivity.


Studies demonstrate a mechanism of resistance to radiation and a chemotherapeutic agent based on a lack of intact downstream biochemical pathways leading to apoptosis rather than a failure to register initial damage or efficiently repair damage.


The authors suggest a therapeutic strategy of identifying agents that at clinically achievable levels are able to override the G2-M division checkpoint and using these agents in conjunction with ionizing radiation (and possibly also agents such as cisplatin) in tumors with impaired p53 function. Methylxanthines with little stimulation to the central nervous system and other checkpoint inhibitors have promise as genome-specific radiosensitizers.


Morphologic and biochemical manifestations of cell death were observed in acute leukemia cells following treatment with a variety of cytotoxic agents of diverse mechanisms of action. Perturbations in the cell cycle were the first changes seen with all agents. Morphologic changes associated with apoptosis was seen with all agents, but the pattern and timing varied with different agents. The authors recommend that investigations of the mechanisms of cell death use several different methodologies (eg, morphology, DNA electrophoresis, flow cytometry, clonogenic survival) rather than rely on a single parameter.


Two competing models for radiation damage to normal tissue have been the depletion of clonogens in the relevant normal tissue and the disruption of normal vascular supply to the organ by radiation killing of endothelial cells. Fibrosis was considered to be a secondary - and largely passive - phenomenon. Using mice that were genetically prone to developing radiation fibrosis, the authors showed that a single radiation fraction was followed by prolonged elevations of inflammatory cytokines such as interleukin 1-alpha, proliferative cytokines such as transforming growth factor-beta, and the expression of collagen mRNA. Radiation-induced cytokines and other proteins in radiation effects, to normal tissues as well as to tumor clonogens, are important additions to our understanding or radiation biology.


It has long been recognized that some patients have severe acute or late complications following radiation therapy. While most of these are idiosyncratic, several syndromes, such as ataxia-telangiectasia (A-T), predictably lead to these outcomes. Since heterozygosity for the A-T gene is common, complications seen in these individuals may impact significantly on our impression of overall radiation-tolerance doses. Radiation-tolerance doses generally are based on uncommon but severe complications. If it can be shown that these are predictable on this or other genetic bases in most cases, it may be possible to safely increase doses to individuals not genetically predisposed to such complications, thus improving the likelihood of local tumor control.


The theme of this article parallels that of the preceding article, but the focus is on toxicity of chemo-therapy rather than radiation therapy. Individuals who sustained severe and persistent sensory and motor neuropathy following modest individual and cumulative doses of vincristine are described. All had a 19p11.2:12 duplication, which is associated with a hereditary motor-sensory neuropathy (Charcot-Marie-Tooth) disease. The authors also raise the possibility that other pre-existing (albeit subclinical) neurologic disorders may predispose individuals to severe drug complications.


The controversy regarding the role of prophylactic cranial irradiation (PCI) for patients with small cell lung cancer hinges on its efficacy and toxicity. There is concern that benefits are counterbalanced by neurologic toxicity that has been attributed to cranial irradiation when administered alone or particularly when given in association with concurrent chemotherapy. This trial suggests no change in psychometric measurements occurred in patients receiving PCI. Thus, late events should not be attributed solely to treatment without knowledge of the patient's pretreatment status and the natural history of the disease process.


The findings reported in this study support the importance of using measures of quality of life in addition to measures of physical toxicity so that patients can make an

The authors demonstrate that telephone-based nursing interventions can enhance patient education. This technique could assist management of the toxicities from combined radiation and chemotherapy for intrathoracic neoplasms.