IN THIS ISSUE

Cancer Immunotherapy Endpoints in Clinical Trials

Cancer immunotherapies act on the immune system rather than directly on tumors and thus may require modified endpoints from radiation therapy and standard chemotherapies. In this review, **Hoos et al. (p. 1388)** describe the initiative of the Cancer Immunotherapy Consortium of the Cancer Research Institute and partner organizations to evaluate and redefine clinical trial endpoints for immunotherapies. The Consortium recommended that T-cell immune response therapy assays be harmonized to minimize data variability, that novel clinical response patterns be incorporated into evaluation criteria, and that new statistical models be considered to assess survival. The authors conclude that these recommendations will potentially improve the planning and implementation of cancer immunotherapy trials.

In an editorial, **Berry (p. 1376)** agrees that different endpoints and statistical methods should be considered for immunotherapy but he argues that this approach is still part of the piecemeal process of drug development. Berry proposes, instead, the development of adaptive trials that use information over the course of the trial to assess hazards and benefits and to give the best balance of risk versus benefit for patients.

Cytosolic Phospholipase A2 and Angiogenesis

Highly angiogenic cancers, including lung cancer and glioblastoma multiforme, are resistant to existing therapies. **Linkous et al. (p. 1398)** investigated the effects of cytosolic phospholipase A2 (cPLA2), which is involved in tumorigenesis and angiogenesis, on these tumors. They looked at the effects of cPLA2 expression in mice that lacked the alpha isoform of cPLA2 and in wild-type mice treated with CDIBA, a chemical inhibitor of cPLA2. They also studied the effect of cPLA2 expression on mouse vascular endothelial cell proliferation and migration. Compared with wild-type mice, cPLA2-deficient mice formed fewer tumors and those tumors had fewer vessels. Treatment of wild-type mice with CDIBA resulted in delayed tumor growth and smaller tumors. cPLA2 deficiency or inhibition with CDIBA reduced vascular endothelial cell proliferation and invasive migration, which were restored by addition of cPLA2-dependent bioactive lipids. The authors suggest that cPLA2 inhibition may be a novel effective antiangiogenic therapy in patients with brain and lung cancers.

In an editorial, **Tosato et al. (p. 1377)** discuss the regulation of tumor angiogenesis by cPLA2 expressed in the tumor microenvironment through the maintenance of pericyte coverage of tumor vessels. They note that unanswered questions include whether cPLA2 directly regulates pericyte function or whether defective pericyte coverage is a result of cPLA2 deficiency in endothelial cells.

Lung Cancer in Postmenopausal Women Using Estrogen Alone

One randomized controlled trial in the Women's Health Initiative (WHI) reported that use of estrogen plus progestin as hormone replacement therapy increased lung cancer mortality. **Chlebowski et al. (p. 1413)** investigated the effects of estrogen only use on incidence and mortality rates for lung cancer among women in another randomized controlled trial within the WHI. In this trial, 10,739 women, aged 50-79 years with a previous hysterectomy, had been randomly assigned to conjugated equine estrogen or placebo. After a mean of 7.9 years of follow-up, lung cancer had been diagnosed in similar percentages of women in both groups (0.15% or 61 women in the estrogen group and 0.13% or 54 in the placebo group) and similar numbers of women had died from lung cancer in both groups. The authors concluded that hormone replacement therapy with estrogen alone did not increase incidence or death from lung cancer.

Hormone-Sensitive Breast Cancers and Alcohol Use

Women who drink alcohol have been found to have increased incidence of breast cancer, but it has been unclear whether they develop certain types of breast cancer more than others. **Li et al. (p. 1422)** used baseline alcohol consumption data from participants in the Women's Health Initiative Observational Study and follow-up data including breast cancer incidence to prospectively examine the risk of postmenopausal breast cancer by subtype. Women who drank alcohol had a greater risk of invasive breast cancer, particularly invasive lobular and hormone receptor-positive tumors, than women who did not drink alcohol. However, they were not statistically at greater risk for ductal and hormone-receptor negative breast cancers.

Targeting Multiple Kinases to Treat HER2-Positive Breast Cancer

Trastuzumab, a humanized monoclonal antibody against the receptor tyrosine kinase, HER2, is used in combination with antineoplastic drugs to treat HER2-positive breast tumors. However, many patients either do not respond to such treatment or relapse quickly. **Seoane et al. (p. 1432)** investigated if trastuzumab showed an increased efficacy when used in combination with dasatinib, a small-molecule tyrosine kinase inhibitor with antitumor properties. The drug combination synergistically inhibited proliferation of HER2-overexpressing breast cancer cell lines, and tumor growth was statistically significantly reduced in mice bearing xenograft tumors originating from HER2-overexpressing breast cancer cells. An investigation of the mechanisms involved showed that the synergistic effect of the trastuzumab and dasatinib combination triggered a DNA damage response and a caspase-independent cell apoptosis.