

RESEARCH HIGHLIGHTS

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Basic Research

Reduced Expression of Survivin May Enhance Antitumor Therapies

Researchers from Eli Lilly and Company in Indianapolis, IN, and ISIS Pharmaceuticals in Carlsbad, CA, presented a study involving downregulation of survivin in human cancer cells. Survivin is an antiapoptosis protein found in most human cancers but not in normal adult tissues. In this study, a survivin antisense oligonucleotide (LY2181308) that inhibited production of the protein was found in lung, colon, pancreas, breast, prostate, ovary, cervix, skin, and brain cancer cells using quantitative reverse transcriptase polymerase chain reaction and Western blot analysis. It also was shown to induce caspase-3–dependent apoptosis, G2/M cell cycle arrest, and multinucleated cells. LY2181308 sensitized tumor cells to chemotherapeutic agents. In a xenograft human tumor model, it showed significant antitumor activity that was associated with inhibition of survivin expression. The researchers concluded that the preclinical data support clinical development of LY2181308 as an anticancer agent.

Inhibitor of Vascular Endothelial Growth Factor Receptor 2 Shows Antitumor Activity in Mouse Model

Many central nervous system tumors demonstrate increased activity of vascular endothelial growth factor receptor and ErbB family proteins. Therapies that target these proteins have been shown to inhibit new blood vessel formation and tumor growth. Researchers from Duke University Medical Center in Durham, NC, and AstraZeneca Pharmaceuticals, LP, in Wilmington, DE, investigated the activity of ZD6472, an orally active inhibitor of vascular endothelial growth factor receptor 2 tyrosine kinase, in athymic nude mice bearing glioblastomas, medulloblastomas, or ependymomas. Significant inhibition of tumor growth was found in all cases compared to the controls. The growth delay ranged from 10.4–25.4 days. In addition, most xenografts showed 10%–

100% regression. Mild weight loss occurred. The tumors showed a decrease in the number of blood vessels, suggesting that ZD6472 had an antiangiogenic effect. The researchers concluded that ZD6472 has therapeutic potential that warrants clinical investigation.

Tumor Cell Circadian Clock Genes May Be New Therapeutic Targets

Circadian coordination of cells within organisms is regulated, in part, by the expression of a series of circadian clock genes. Optimal circadian drug delivery has been shown to possibly improve outcomes for patients with ovarian cancer, acute childhood leukemia, and metastatic colorectal cancer. Researchers from the University of South Carolina in Columbia investigated the influence of tumor cell circadian clock gene expression on cancer cell functions essential for tumor growth. In their study, 30 female C3H/HeJ mice were kept on a 12-hour light and 12-hour dark schedule. The mice were injected with syngeneic mammary tumor cells at a single time of day, and minimally invasive measurements of the tumor growth rate were made over many days. The tumor growth rate was nearly doubled during the daily activity/dark circadian phase compared to the sleep/light phase. Mice were euthanized during the diestrous or late follicular phase of their estrous cycles at one of six equispaced circadian stages (5 mice per group). Livers and tumors were examined for RNA expression of circadian clock genes. The results showed that normal liver tissue and tumor tissue from tumor-bearing mice retained circadian clock gene expression. The circadian clock gene expression pattern was similar to that in the nontumor-bearing mice. The researchers suggested that circadian clock genes may be novel anticancer targets.

Clinical Research

Molecular Marker Phenotype May Be a Prognostic Factor for Head and Neck Cancer

Researchers from the Gray Cancer Institute, Mount Vernon Hospital, and University College London, all in London, England, and the Barbara Ann Karmanos Cancer Institute in Detroit, MI, presented the results of a study examining molecular markers in head and neck squamous cell carcinomas. Patients (N = 402) were randomized into study arms receiving continuous hyperfractionated accelerated radiation therapy (CHART) or conven-

tionally fractionated radiation therapy (CRT). Patient survival, distant metastases, local tumor control, and nodal recurrence were examined. Immunohistochemistry was used to examine tissues for the presence of Ki-67 (a marker of cell proliferation), p53 (a tumor suppressor protein), and bcl-2 (a protein involved in apoptotic pathways). In this study, cluster and Cox survival analysis permitted identification of groups of patients who responded differentially to the treatment arms. Patients with tumors that showed mostly organized Ki-67 staining, absent p53 staining, and negative bcl-2 staining had local control and survival benefit from CHART. Those who had tumors that highly expressed Ki-67 with a random pattern, absent p53 staining, and negative bcl-2 staining did not benefit from CHART. Significantly better than average response to CHART and CRT was found for patients with bcl-2–positive tumors. These patients demonstrated 67% and 68% local control, 75% and 82% metastasis-free disease, and 56% and 67% five-year survival for the CHART and CRT arms, respectively. The researchers concluded that molecular phenotypes may be useful for determining appropriate treatment for patients with head and neck cancers.

[F-18]-Fluoroestradiol Positron Emission Tomography May Predict Breast Tumor Response to Therapy

Researchers from the University of Washington in Seattle presented the results of a study of [F-18]-fluoroestradiol (FES) uptake measured by positron emission tomography (PET) for patients with recurrent or metastatic breast cancer from estrogen receptor (ER-) positive primary tumors treated with hormonal therapy. Breast tumors with high levels of ER respond to hormonal therapy, and those with low levels do not. Furthermore, recurrent tumors may have low levels of ER even though the initial tumor had high expression. Data were analyzed for 34 patients. Of these, more than 50% had received prior tamoxifen therapy. All patients had discontinued therapy for more than two months prior to the study. The participants first underwent FES PET and then were treated with hormonal therapy, primarily aromatase inhibi-

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tors, without other chemotherapy for at least six months (unless tumor progression occurred). The average FES uptake was calculated, and patient response was evaluated by clinical follow-up, tumor markers, and imaging. The Kruskal-Wallis rank-sum test was used to determine the association between FES uptake and response. FES uptake was shown to predict response. No patient with low FES uptake had an objective response. For patients whose disease progressed despite high FES uptake, more than half showed high levels of HER2 expression. The researchers concluded that FES uptake can predict the likelihood of response to hormonal therapy and the interaction with other growth factor pathways should be investigated.

Research Highlights From the 26th Annual San Antonio Breast Cancer Symposium San Antonio, TX December 3–6, 2003

Clinical Research

Clinical Stage T3 Breast Cancer Lymph Node Involvement May Predict Local Recurrence

Researchers at the University of Texas M.D. Anderson Cancer Center in Houston retrospectively reviewed clinical data for 132 patients with stage I or II breast cancer who were treated with neoadjuvant chemotherapy and mastectomy without radiation. The median age was 49 years, and clinical stages at diagnosis were I (5%), IIA (46%), and IIB (49%). Patients were treated with either a doxorubicin-based regimen or single-agent paclitaxel. At 47 months follow-up, factors that correlated with local regional recurrence were clinical stage T3 N0 ($p = 0.0057$), four or more positive lymph nodes at surgery ($p = 0.0001$), age less than or equal to 40 years at diagnosis ($p = 0.0001$), and no use of tamoxifen. Estrogen-receptor-positive disease correlated with local regional recurrence for patients who did not take tamoxifen ($p = 0.0067$). The researchers concluded that T3 primary disease, four or more positive lymph nodes, and young age are predictive of local regional recurrence for patients with stage II breast cancer. For those who have one to three positive lymph nodes, the five-year risk of local regional recurrence is low and does not justify routine postmastectomy radiation.

Breast Tumor Molecular Profiles May Predict Response to Tamoxifen

Researchers from the Netherlands examined 70 breast tumor samples from patients with advanced disease prior to treatment with tamoxifen. Thirty of these patients achieved

an objective response, and 40 had progressive disease. Microarray technology was used to identify 8,600 potentially relevant genes. Further analysis of 50 tumor samples using bioinformatics software narrowed the relevant genes to 143 that were differentially expressed in tamoxifen-responsive and -sensitive tumor samples. Additional analysis reduced the set to 40 genes that correctly predicted the outcome for 96% of the 50-patient sample. The 40-gene predictive set subsequently was shown to correctly predict treatment outcome in 80% of a small set of 15 tumors. A larger study currently is under way. The researchers concluded that gene expression profiles could be used to predict objective responses to tamoxifen.

Pretreatment and Pathologic Parameters May Predict Breast Cancer Recurrence

Researchers at the University of Texas M.D. Anderson Cancer Center in Houston presented the results of a study to determine locoregional recurrence of breast cancer after neoadjuvant chemotherapy and breast-conserving therapy. Tumor and patient characteristics of 362 patients with breast cancer were examined. In the patient sample, clinical cancer stage at diagnosis was I (4%), IIA (24%), IIB (33%), IIIA (25%), IIIB (8%), or IIIC (7%). Kaplan-Meier analysis was used to calculate rates of local recurrence, ipsilateral breast tumor recurrence, and distant metastasis-free survival. At a median follow-up period of 65 months, the pretreatment and pathologic parameters that positively correlated with disease recurrence were clinical N2 or N3 stage ($p = 0.009$), pathologic tumor size greater than 2 cm ($p = 0.009$), multifocal pattern of residual disease ($p = 0.005$), and lymphovascular space invasion in the tumor sample ($p = 0.002$). Each of these factors independently predicted local recurrence and ipsilateral breast tumor recurrence using a Cox logistic regression analysis. The researchers concluded that breast-conserving therapy results in acceptably low rates of disease recurrence in appropriately selected patients.

Basic Research

Gefitinib or Trastuzumab May Restore Tamoxifen Sensitivity in HER2-Overexpressing Tumors

A mouse xenograft model for human breast cancer that overexpressed HER2 was developed by researchers at Baylor College of Medicine in Houston, TX, and AstraZeneca Pharmaceuticals, LP in Wilmington, DE. The researchers previously had shown that treatment of these mice with tamoxifen stimulated tumor cell growth, suggesting

that overexpression of HER2 resulted in drug resistance. They also found that drug resistance could be reversed by treating the mice with gefitinib (Iressa®, AstraZeneca Pharmaceuticals, LP), an inhibitor of the epidermal growth factor receptor/HER2 pathway. The efficacy of trastuzumab (Herceptin®, Genentech, Inc., South San Francisco, CA) and gefitinib was compared as single or combination agents. Trastuzumab is a monoclonal antibody that inhibits the HER2 pathway potentially through a different mechanism compared to gefitinib. Tumors were established in the mice in the presence of continuous estrogen. Mice were randomized into either a continuous estrogen group or a tamoxifen group. Each of the two groups was further randomized into one of four treatment arms: control (vehicle only), gefitinib, trastuzumab, or both. In the tamoxifen group, gefitinib completely blocked tamoxifen-stimulated growth and stabilized tumors ($p < 0.001$). Tumor volume was reduced by 30% or less. However, in the trastuzumab group, tumor volume was reduced by 70% or more. The median time to resistance was prolonged significantly in the trastuzumab group (146 days) compared to the gefitinib group (98 days). The researchers suggested that the combination of gefitinib and trastuzumab might prolong the median time to resistance because at the time of the report (153 days) the median time to resistance had not yet been reached. In the continuous estrogen group, gefitinib, trastuzumab, or the combination had only a minimal inhibitory effect on tumor growth. The researchers concluded that treatment with combined gefitinib and trastuzumab may be a valid clinical strategy for patients with tumors that overexpress HER2.

Active Immunotherapy May Treat HER2-Positive Breast Tumors

Researchers from the University of Vienna in Austria presented the results of a study designed to develop an active vaccine that could be used for breast cancer immunotherapy. They tested peptides that mimic the epitope (mimotopes) of the growth-inhibitory antibody trastuzumab. Five candidate mimotopes were obtained from a screen using trastuzumab. The mimotopes were recognized by the antibody with high specificity, although their amino acid sequence was not similar to the HER2 protein. Two mimotopes that were determined to be “the best” were conjugated with the immunogenic carrier, tetanus toxoid. The conjugates were recognized specifically by trastuzumab. Immunization of Balb/c mice with the conjugate resulted in the production of antibodies that recognized HER2. The researchers concluded that active mimotope immunotherapy may be useful as a novel concept for breast cancer treatment.