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175 GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

Role of BRCA1 in Response to Therapeutic DNA-Damaging Agents in Human Breast Cancer Cells. *D. L. Maresco, P. Arnold, F. Bogomolniy, L. Norton, P. Borgen, J. Boyd; Memorial Sloan-Kettering Cancer Center, New York, NY*

Introduction: BRCA1, a tumor suppressor of breast and ovarian cancer, functions in the repair of DNA damage. In mouse cells, BRCA1 has been shown to repair double-strand DNA breaks. In human cells, BRCA1 associates with numerous DNA repair proteins. Furthermore, the human breast cancer cell line HCC1937, which contains a mutant BRCA1, is hypersensitive to radiation and to the DNA-damaging agent methyl methanesulfonate. In an effort to better design therapeutic regimens for BRCA1-associated cancers, we sought to determine whether BRCA1-deficient cancer cells are more sensitive to therapeutic agents that cause double-strand breaks than are cancer cells with wild-type BRCA1. Methods: We tested the cytotoxic effect of a broad panel of therapeutic agents, using the HCC1937 cell line, two breast cancer cell lines wild-type for BRCA1 (SK-BR-3 and MCF7), and an MCF7 BRCA1 antisense clone. Both cell proliferation and colony-forming assays were used. Results: As expected, HCC1937 cells were not hypersensitive to paclitaxel, which does not cause DNA damage, and were hypersensitive to ionizing radiation. Unexpectedly, HCC1937 cells were not hypersensitive to two chemotherapeutic agents that induce double-strand DNA breaks (doxorubicin and etoposide). HCC1937 cells were, however, significantly hypersensitive to Mitomycin C and, as others have recently shown in rodents, to cisplatin, both of which induce intrastrand and interstrand DNA crosslinks. The MCF7 BRCA1 antisense clone was markedly more sensitive to cisplatin than MCF7 parental cells. Conclusion: These data suggest that human BRCA1-deficient breast cancer cells are hypersensitive to therapeutic agents that cause DNA crosslinks but not to agents that cause double-strand DNA breaks or to paclitaxel. Additionally, our finding that an MCF7 BRCA1 antisense clone has increased sensitive to cisplatin more strongly correlates BRCA1 with sensitivity of breast cancer cells to DNA crosslinking agents. These findings provide insight into the role of BRCA1 in DNA repair by linking BRCA1 to a specific type of DNA damage repair and may lead to the development of better chemotherapeutic regimens for BRCA1-associated cancers.

176 GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

Analysis of HER1 and HER2 in the Heart to Clarify the Cardiotoxicity of Herceptin. *I. B. Fuchs, S. Landt, H. Buehler, K. Evers, A. Kleine-Tebbe, W. Lichtenegger, G. Schaller; Charité Campus Virchow-Klinikum, Berlin, Germany; Benjamin Franklin Medical Center, Berlin, Germany*

Powerful combination therapy applying the HER2 antibody Herceptin™ with anthracyclines in the management of HER2-overexpressing metastatic breast cancer is limited by severe cardiotoxic side effects. HER2 is one of four members of the epidermal growth factor receptor family, which elicit its intracellular response by dimerization with HER1 or other family members. In vivo experiments in rodents indicate that HER2 plays an essential role in cardiogenesis and myocardial protection. To clarify, if direct antibody interaction with heart tissue contributes to the cardiotoxicity of Herceptin™ we analyzed pathologically altered myocardium for the presence of HER 1 and HER2. Sixty heart biopsies from patients with cardiac dysfunction revealed histological alterations ranging from myocarditis to severe myocardial hypertrophy. Moreover myocardium of 25 breast cancer patients with or without previous anthracycline treatment was assessed. Immunohistochemical analyses were performed using the primary antibody AB.10 (NeoMarkers) for HER1 expression and the HercepTest (DAKO) for HER2 expression. In specimens showing a faint HER2 signal staining was repeated using an amplifying fluorescent Cy3 detection. HER2 gene amplification was analyzed by fluorescence in situ hybridisation (FISH) (Inform-Kit, Ventana). Neither in the heart biopsies of the cardiac patients nor in the myocardium of the breast cancer patients HER1 expression was noticed. Immunohistochemical detection of HER2 expression revealed a faint discontinuous membrane staining in a few biopsies, which resulted in a distinct spottet staining of total membranes with the intensified fluorescent Cy3 labelling. A strong staining typical for HER2-overexpressing breast cancer was not found. There was no HER2 gene amplification detected by FISH. Since we could not detect a strong expression of HER1 and HER2 in the myocardium, a direct interaction of the HER2 antibody Herceptin™ with the myocardium seems unlikely to be responsible for the cardiotoxicity of Herceptin™. Indirect mechanisms as like a Herceptin™-induced increase of cytokines should, therefore, be taken in consideration.

177 GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

Canalicular Stenosis is the Mechanism for Excessive Tearing in Patients on Weekly Docetaxel. *B. Esmaeli, D. Booser, M. Ahmadi, V. Valero, N. Ibrahim, G. Hortobagyi, R. Arbuckle, E. Delpassand, F. Esteva; Univ. of Texas M.D. Anderson Cancer Center, Houston, TX*

Docetaxel is a widely used antineoplastic agent for advanced breast cancer and other malignancies. The toxicity profile for weekly docetaxel is different from every-three-weeks docetaxel. In particular, the symptom of epiphora (excessive tearing) has been reported in a higher percentage of patients receiving weekly docetaxel (50%) compared with the every-three-weeks regimen (10%). However, the mechanism for epiphora has not been previously described. We reported 14 patients on weekly docetaxel who had canalicular stenosis as the underlying mechanism for epiphora. Three patients received weekly docetaxel as a single agent; the rest received docetaxel and herceptin or adriamycin. The length of time to development of epiphora ranged from 4–16 weeks (mean =7 weeks). Bicanalicular silicone intubation or dacryocystorhinostomy (DCR) to overcome the lacrimal outflow blockage was recommended in all 14 patients. Complete or near complete resolution of epiphora was accomplished in 11 patients who underwent surgery. To determine the relative frequency of canalicular stenosis, we evaluated 19 additional patients enrolled in a weekly docetaxel and Herceptin protocol and 18 patients enrolled in an every-three weeks docetaxel and adriamycin protocol. Ten patients in the weekly docetaxel/Herceptin protocol had significant canalicular stenosis and required surgical intervention. Although many patients on every-three-weeks docetaxel/Adriamycin had transient epiphora, none had significant anatomic narrowing of the canaliculi. In summary, we describe canalicular stenosis as a newly recognized mechanism for excessive tearing secondary to docetaxel. Canalicular stenosis is much more common with weekly docetaxel than with the every-three-weeks regimen and can persist after cessation of therapy. Timely diagnosis of canalicular stenosis can prevent complete closure of the canaliculi by allowing for bicanalicular silicone intubation early in the course of weekly docetaxel administration. Prospective studies are under way to confirm our observations and to identify the incidence of canalicular stenosis in patients receiving weekly docetaxel.

178 GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

Preliminary Results of a Randomized Double-Blind Phase II Study of the Selective Estrogen Receptor Modulator (SERM) Arzoxifene (AZ) in Patients (Pts) with Locally Advanced or Metastatic Breast Cancer (MBC). *A. U. Buzdar, J. O'Shaughnessy, C. Hudis, D. Booser, J. Pippen, S. Jones, P. Munster, N. Enas, A. Melemed, E. Winer, A. Storniolo; M.D. Anderson Cancer Center, Houston, TX; US Oncology, Dallas, TX; Memorial Sloan-Kettering Cancer Center, New York, NY; Eli Lilly and Company, Indianapolis, IN; Dana-Farber Cancer Institute, Boston, MA*

AZ is a new selective estrogen receptor modulator (SERM) shown to be antagonistic in preclinical breast and endometrial models while agonistic on bone and lipids. Phase I testing identified an active dose range and a multi-institutional randomized, phase II trial was conducted to evaluate the safety, toxicity, and efficacy in two dose levels (20 mg or 50 mg daily) of AZ in pts with advanced or MBC. Pts had either tamoxifen (tam) sensitive (TS) or refractory (TR) disease. TS was no prior tam or relapsed 12 months since adjuvant tam; all other pts were TR. A total 119 pts were randomized, 63 were TR and 49 TS. For 63 TR pts, the median (med) age was 58 years, 83% were postmenopausal; med time from diagnosis to study entry was 4 yrs (range 1–25), 57% of pts had prior adjuvant chemotherapy, 46% and 54% of pts had received prior adjuvant/palliative hormonal therapy, respectively. Among the 49 TS pts, med age was 56 years, 84% were ER+, and 84% were postmenopausal; med time from diagnosis to study entry was 6 years (range 0–34), 29% of patients had received prior tam, and 50% had received adjuvant chemotherapy. The combined ORR for the TR cohort was 7%, and 12% of patients had clinical benefit (CB) (CR+PR+SD≥6 mo). The combined ORR for the TS cohort was 16%, with a CB of 33% (See Table-Intent to treat analysis for each cohort). There were no significant differences in response rates, time-to-progression, or toxicity, between the 20 and 50 mg subgroups. Overall, hot flashes and nausea were reported in 43% and 21% of patients. AZ was well tolerated and effective in tam-sensitive pts in this multi-institutional phase II study. Less activity was seen in the TR pts. In a multinational phase III study efficacy and safety of AZ 20 mg/day is being compared with tamoxifen in TS patients.

Table.

Cohort	Dose	pt #	PR #	SD #	ORR	CB	TTPD
TS	20 mg	24	6	2	26%	33%	5.5 mo
TS	50 mg	25	2	6	8%	32%	3.1 mo
TR	20 mg	31	2	1	6%	10%	2.7 mo
TR	50 mg	32	2	2	6%	13%	2.8 mo