1228 POSTER

Avemar Lyophilisate, a Proprietary Fermented Wheat Germ Freeze-dried Extract Inhibits Breast Cancer Cell Proliferation and Invasion in Vitro

Z. Bago-Horvath[1], M. Teichmann[1], B. Forstner[2], O. Komina[3], A. Bedeir[3], J. Wesierska-Gadek[3], M. Grusch[3], T. Szekeres[4], G. Krupitza[1], R.M. Mader[2]. *[1]Medical University of Vienna, Clinical Institute of Pathology, Vienna, [2]Medical University of Vienna, Department of Medicine I Division of Oncology Comprehensive Cancer Center, Vienna, [3]Medical University of Vienna, Department of Medicine I Division of Oncology Institute of Cancer Research Comprehensive Cancer Center, Vienna, [4]Medical University of Vienna, Clinical Institute of Medical and Chemical Laboratory Diagnostics, Vienna, Austria*

Background: Avemar, a fermented wheat germ extract has been demonstrated to inhibit metastatic tumour spread and prolong survival in colorectal cancer and melanoma patients. In the present study, the antiproliferative and antimigratory effects of the fermented wheat germ freeze-dried extract (Avemar lyophilisate) have been investigated in breast cancer cells using a 3D-carcinoma-lymphendothelial-cell co-culture model.
Materials and Methods: MCF-7 estrogen-receptor expressing and HCC-1937, MDA-MB-231 and MDA-MB-468 estrogen-receptor negative breast cancer cells were incubated with increasing concentrations of Avemar lyophilisate. Cell cycle phase disribution was determined by flow cytometry. Caspase 3/7 and 8-dependent induction of apoptosis was analyzed by chemiluminescence. To elucidate the antimigratory and antiinvasive effects of Avemar lyophilisate, a 3D co-culture model of MCF-7 tumour cell spheroids and lymphendothelial cells was utilized. The expression of motility-associated proteins was analyzed by Western blotting.
Results: Avemar lyophilisate arrested luminal-type MCF-7 cells in the S phase of the cell cycle, whereas basal type breast cancer cells underwent an G0-G1 arrest in a dose-dependent manner after treatment with 100–400 μg/ml Avemar lyophilisate. Induction of apoptosis was mediated by caspase 3/7 in HCC-1937, MDA-MB-231 and MDA-MB-468, whereas in MCF-7 cells, caspase 8 was preferentially cleaved. In a 3D co-culture model, Avemar lyophilisate significantly inhibited lymphendothelial motility, and reduced tumour spheroid induced gap size by 43%. Western blotting revealed regulation of several proteins involved in cell motility, such as paxillin.
Conclusions: Avemar lyophilisate exerts differential effects in luminal and basal type breast cancer cells and is able to inhibit cellular processes involved in tumour cell invasion and lymphatic spread. Therefore, further *in vivo* and clinical studies investigating the antitumour effects of this natural compound in breast cancer are warranted.

1229 POSTER

Effect of Green Tea Extracts on Oxaliplatin-induced Peripheral Neuropathy in Rats

E.K. Jeon[1], J.S. Lee[2], W.T. Kim[2], H.S. Won[1], Y.S. Cho[3], Y.H. Ko[1]. *[1]Uijongbu St. Mary's Hospital, Division of Oncology Internal Medicine, Uijongbu City, [2]Uijongbu St. Mary's Hospital, Rehabilitation Medicine, Uijongbu City, [3]Uijongbu St. Mary's Hospital, Division of Gastroenterology Internal Medicine, Uijongbu City, Korea*

Background: Green tea contains four polyphenol catechins, which are known to be potent antioxidants. We conducted an animal experiment to determine whether green tea extracts have neuroprotective effects on oxaliplatin-induced neurotoxicity.
Material and Methods: Adult rats were given oxaliplatin (4 mg/kg) twice weekly and green tea extracts (300 mg/kg) once daily for 6 weeks, while the control animals received only oxaliplatin. Behavioral and electrophysiological tests were conducted before oxaliplatin administration and at 2, 4, and 6 weeks following oxaliplatin administration.
Results: At 4 and 6 weeks, sensory threshold values were significantly decreased in oxaliplatin-treated rats compared with those in oxaliplatin + green tea extract-treated rats (4 and 6 weeks; $P = 0.01$ and $P = 0.01$, respectively), but no difference in thermal threshold values was found between the two groups during the experimental period. The electrophysiological assessment revealed no significant change in the two groups during the experimental period. TUNEL staining showed no significant difference in the number of apoptotic-featured cells between the two experimental groups in the dorsal root ganglia or peripheral nerves, but the number of apoptotic-featured cells in dorsal root ganglia was higher than that in sciatic nerves within each group.
Conclusions: Green tea extracts may be a useful adjuvant to alleviate sensory symptoms, such as allodynia, in the early stages of neurotoxicity in clinical settings.

1230 POSTER

A Phase 1 and Pharmacokinetic Study of Ganetespib (STA-9090), a Heat Shock Protein 90 Inhibitor, in Combination With Docetaxel in Subjects With Advanced Solid Tumour Malignancies

R.D. Harvey[1], C.M. Lewis[1], J.S. Kauh[1], T.K. Owonikoko[1], A. Akintayo[1], M. Karol[2], F. Teofilovici[2], J.M. Lufkin[2], F.R. Khuri[1], S.S. Ramalingam[1]. *[1]Winship Cancer Institute of Emory University, Department of Hematology and Medical Oncology, Atlanta GA, [2]Synta Pharmaceuticals, Clinical Development, Lexington MA, USA*

Background: Ganetespib is a potent, next-generation Hsp90 inhibitor that is structurally unrelated to the first-generation ansamycin class of Hsp90 inhibitors and has shown superior activity to these agents in preclinical studies. Ganetespib has been well tolerated and has shown promising single-agent antitumour activity in early trials in multiple cancers. Based on preclinical synergy between ganetespib (G) and docetaxel (D), a phase I pharmacokinetic (PK) and feasibility study was initiated with the combination.
Materials and Methods: Patients (pts) with advanced solid tumour malignancies and ECOG performance status (PS) 0−2 were eligible. Sequential cohorts of pts were treated (3+3 design) with increasing doses of D (day 1) and G (days 1, 8) administered as an 1-hr separate infusion in a 3-week cycle. PK sampling was performed on days 1/8 of cycle 1. The primary endpoint was determination of optimal doses of the two agents for combination therapy.
Results: Thirteen pts were enrolled in the dose escalation phase. Median age-63 (44−72); 2-M, 11-F; ECOG PS 0−1, 1, 12. At dose levels 1 (D-60 mg/m^2, G-150 mg/m^2) and 2 (D-75 mg/m^2, G-150 mg/m^2), none of 6 pts initially treated had a DLT. Two of 4 pts at dose level 3 (D-75 mg/m^2, G-200 mg/m^2) had DLTs (g4 febrile neutropenia and one g4 neutropenia of >7 days), requiring expansion of dose level 2. As no other DLTS were observed; level 2 was the expansion cohort. Common AEs included neutropenia (n = 10), diarrhea, anemia and fatigue (n = 4 each), nausea and febrile neutropenia (n = 3 each). Common g 3/4 AEs included neutropenia (n = 10) and febrile neutropenia (n = 3). The median number of cycles received is 4 (1−8), with 6 pts still on study. Among 10 pts evaluable for response, 7 had disease stabilization following cycle 2 (6 weeks), 4 pts to 12 weeks and 1 pt to 18 weeks. PK data from dose level 1 indicates PK similarity between G administered alone and G administered prior to D. No drug accumulation was observed following once-weekly dosing which is consistent with other studies where G was administered alone. Additional PK data will be presented.
Conclusions: The combination of docetaxel and ganetespib is well tolerated at the recommended doses of 75 mg/m^2 and 150 mg/m^2. Promising anti-cancer activity was noted, and a randomized phase II study of the combination has been initiated in advanced NSCLC.

1231 POSTER

Radiolabeled Iodohypericin as Tumour Necrosis Avid Tracer − Diagnostic and Therapeutic Potential

T. Marysael[1], M. Van de Putte[1], H. Fonge[1], M. Miranda Cona[2], J. Li[2], G. Bormans[1], A. Verbruggen[1], Y. Ni[2], P. de Witte[1]. *[1]Katholieke Universiteit Leuven, Pharmaceutical Sciences, Leuven, [2]Katholieke Universiteit Leuven, Medical and Diagnostic Sciences, Leuven, Belgium*

Background: It is estimated that 30% to 80% of solid tumour mass represents necrotic tissue that consists out of a significant number of dead and dying cells. The fact that these necrotic zones are restricted to dysplastic and malignant tissue and are rarely present in normal tissue makes necrosis an interesting target both for cancer diagnosis and therapy. In this study, the avidity of hypericin (HYP), [^{123}I]iodohypericin (^{123}I-HYP) and [^{131}I]iodohypericin (^{131}I-HYP) to tumour necrosis was explored for both diagnosis and therapy of experimental malignancies.
Materials and Methods: All experiments were performed on female athymic nude BALB/c mice, dorsally inoculated with 2×10^6 radiation induced fibrosarcoma (RIF-1) tumour cells. Radiolabeled derivatives were synthesized by electrophilic radioiodination using Na[^{123}I]iodide (13.7 GBq/ml in 0.05 M NaOH) and Na[^{131}I]iodide (7.4 GBq/ml in 0.05 M NaOH). Compounds were purified on HPLC coupled with a radiometric detector (3-inch NaI(Tl) crystal).
To evaluate the intratumoral distribution of HYP and ^{123}I-HYP, autoradiography, fluoromicroscopy and planar gamma scintigraphy were performed. A therapy study was performed to assess the antitumoral effect of ^{131}I-HYP. An overview of the parameters used for the respective techniques is given in the table.