1228 POSTER

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

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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

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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

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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

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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.

	Tumour size	Compound used	Dosage	Time points
Autoradiography	Small	^{123}I-HYP	100 μCi/mouse (n = 5)	4h, 24h p.i.
Fluorescence microscopy	Small	HYP	10 mg/kg (n ⩾ 3)	6h, 24h, 48h, 72h p.i.
Planar gamma scintigraphy	Bulky	^{123}I-HYP	170 μCi/mouse (n = 5)	30h, 55h p.i.
Therapy study			control: saline at day 0, 6, 13 (n = 6)	*day 0, 6, 13, 18 **day 24
(*FDG micro-PET)	Small	^{131}I-HYP	group 1: 300 μCi at day 0, 6, aline at day 13 (n = 6)	*n/a **day 24
(**Autoradiography)			group 2: 300 μCi at day 0, 6, 13 (n = 6)	*day 13, 18 **day 24

Results: The intratumoral distribution in RIF-1 tumours was investigated by means of fluorescence microscopy (HYP) and autoradiography (^{123}I-HYP). Results show high uptake of the tracers in necrosis at 24 h, lasting for up to 72 h p.i. Ratios of activity of ^{123}I-HYP in necrotic tissue over viable tumour reached up to 19.63±4.66, correlating with 9.20% ID/gram in necrosis. Nude mice bearing RIF-1 tumours that received 3 injections of 300 μCi over a 3-week treatment period showed stabilization in tumour growth for 5 days, as measured by caliper and micro-positron emission tomography using [^{18}F]fluorodeoxyglucose.
Conclusion: Based on these results, we suggest the potentials of radiolabeled hypericin 1) in diagnostic aspects including prognosis or staging assessment of bulky necrotic cancers, monitoring of treatments and therapeutic follow-up; and 2) in cancer treatment based on tumour necrosis. In conclusion, we showed that hypericin radiolabelled with iodine is a necrosis avid tracer that can be used both as a tumour diagnostic and therapeutic.

1232 POSTER

Creatinine Clearance (CrCl) as a Predictive Marker for the Risk of Toxicity From Molecularly Targeted Agents (MTA) in Phase I Trials

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Background: Phase I trials are designed to define toxicity and maximum tolerated dose of a new drug. Molecularly targeted agents (MTAs) are primarily administered orally at a flat dose independent of patient height, weight and creatinine clearance (CrCl). The aim of this study was to evaluate for a correlation between both baseline CrCl and body surface area (BSA) and the development of grade (gr) 3 and 4 toxicities during the first course of therapy within a phase I trial.
Materials and Methods: A retrospective analysis was performed on all patients (pts) treated within phase I trials at the Royal Marsden Hospital, between January 2005 and December 2009. Data collected included all gr 3/4 toxicities possibly related to the drug, dose and laboratory assessments including serum creatinine, height and weight. CrCl was calculated using Cockroft-Gault (CG) formula and Modification of Diet in Renal Disease (MDRD) formula.
Results: 960 pts were included for the analysis. Median age: 59 years; 54% were male. 80% received single agent MTA, 17% received MTA in combination with classic cytotoxic (CTX) therapy and 3% received single agent novel CTX. 226 patients (23%) developed at least one episode of gr 3/4 toxicity and four patients (0.4%) experienced gr 5 toxic deaths. In pts developing toxicity, mean CG and MDRD were 90 and 74 ml/min compared with 100 and 78 ml/min for pts without toxicity (p = 0.002 and p = 0.016) respectively. A CG >120 ml/min was associated with a significantly lower risk of toxicity (14% vs. 25%) compared to a CG <120 ml/min (p = 0.001). Multivariate logistic regression analysis showed that CrCl was an independent variable that influenced gr 3/4 toxicity (OR = 0.99 [95% CI 0.98–0.99]). BSA did not correlate with risk of toxicity.

Table 1. Toxicity according to agent received and creatinine clearance by Cockroft-Gault (CG)

CG	MTA		CTX	
	G3/4 Toxicity	No Toxicicty	G3/4 Toxicity	No Toxicity
>120	14 (9.6%)	132 (90.4%)	11 (34.4)	21 (65.6%)
120–100	14 (13.2%)	92 (86.8%)	20 (55.6%)	16 (44.4%)
100−60	65 (18.9%)	279 (81.1%)	46 (49.5%)	47 (50.5%)
<60	18 (24%)	57 (76%)	6 (42.9%)	8 (57.1)
Total	111 (16.5%)	560 (83.5)	83 (47.4%)	92 (52.6)
	P = 0.016		*P* = 0.33	

Conclusions: Within the constraints of phase I trials where pts with a creatinine of >X1.5 the upper limits of normal are excluded, the risk of gr 3/4 toxicities is associated with a lower CrCl. CrCl calculated by CG is a valuable tool that can be utilized to predict the risk of significant toxicity with MTAs in phase I trials.

1233 POSTER

Phase I/II Study With Trabedersen (AP 12009) Monotherapy for the Treatment of Patients With Advanced Pancreatic Cancer, Malignant Melanoma or Colorectal Carcinoma

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Background: TGF-β2 overexpression in solid tumours triggers key cancer pathomechanisms, particularly immunosuppression and metastasis. The antisense oligonucleotide trabedersen specifically inhibits TGF-β2 expression. This study evaluates the MTD, safety, pharmakokinetics, and efficacy of i.v. trabedersen treatment in patients with advanced solid tumours.
Methods: This open label, multicenter, Phase I/II study enrolled a total of 61 patients. Of these, 33 patients with pancreatic carcinoma (PanCa, stage III/IV, N = 23), malignant melanoma (MM, stage III/IV, N = 5), or colorectal carcinoma (CRC, stage III/IV, N = 5) were enrolled during dose-escalation. Patients were treated in cohorts with i.v. trabedersen monotherapy as 2nd to 4th-line therapy with escalating doses in 2 treatment schedules (1st schedule: 7d on, 7d off; 2nd schedule: 4d on, 10d off; up to 10 cycles). Within the 1st schedule, the MTD was established at 160 mg/m^2/d. In the 2nd schedule dose-escalation was stopped before reaching an MTD. A well tolerated dose (140 mg/m^2/d) with encouraging efficacy was identified. An additional cohort of 14 patients with MM or PancCa each was treated with this dose and schedule (140 mg/m^2/d; 4d on, 10d off).
Results: Trabedersen was safe and well-tolerated. The only expected adverse reaction identified was transient thrombocytopenia (max. NCI-CTC grade 3).
The mOS of all PanCa patients treated 2nd-line (independent of dose and schedule, N = 15) was 6.9 months [95% CI: 2.9, 13.4], while the mOS of PanCa patients treated with the 2nd schedule-140 mg/m^2/d regimen (N = 9) was 13.4 months [95% CI: 2.2, 39.7]. One PanCa patient (treated 3rd line) had a complete response of liver metastases and is still alive after 61 months (as of Oct2010).
Promising efficacy data were also seen in 4 of the 5 MM patients during dose-escalation: one patient with metastatic and DTIC-resistant melanoma is still alive 25.5 months after start of treatment; 3 other patients with stage IV melanoma, treated 3rd or 4th-line with trabedersen survived for 11.4, 13.8, and 18.6 months (as of Feb2011).
Conclusions: Trabedersen showed good safety and encouraging survival. The follow-up of 14 MM patients treated with the 4d on, 10d off-140 mg/m^2/d regimen is ongoing. A randomized, active-controlled Phase II/III study in PanCa patients is in preparation.

1234 POSTER

A First in Man Phase 1 Study of JNJ-26481585, a Novel Oral Histone Deacetylase Inhibitor (HDACi) in Advanced Cancer Patients − Evidence of Target Modulation, Antitumour Activity and Additional Safety Data in an Expanded Patient Cohort

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Background: JNJ-26481585 is a potent, hydroxamate, pan-HDACi with extensive tissue distribution, improved PD parameters and broad activity in solid and hematologic tumour models.