with the rounds and 36% were familiar. Fifty-nine percent attended the rounds a few times per year and 28% attended every month. Forty-three percent were very satisfied with the educational content and 54% were satisfied. Sixty-one percent of the respondents were very satisfied with the speakers and 36% were satisfied. Fifty percent of the respondents very rarely returned the evaluation forms and 32% returned the evaluation forms frequently. Lists of the topics for the next year's sessions, as well as the likelihood of attendance, were suggested.

Conclusion: Our Continuing Education program was highly evaluated by the multidisciplinary audience. Several suggestions for continuation and improvement of this program will be discussed at the conference with the detailed analysis of the data.

541 POSTER

The advantage of proton therapy for soft tissue tumours in childhood

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Background: In paediatric radiotherapy, the reduction of dose to all normal tissues is essential to reduce potential late side effects. For children with soft tissue tumours treated with protons at PSI, a comparative treatment planning study has been undertaken comparing these treatments with what could be possible with Intensity Modulated Photon Therapy (IMRT).

Materials and Methods: Seven children were treated with protons at PSI for soft tissue tumours between 1997 and 2002. For each case, IMRT plans have been calculated and compared to the delivered proton dose distributions. Criteria for the comparison were integral dose to the non-target normal tissues, mean doses to selected organs at risk (OARs) and the irradiated volume at 50%.

Results: The median age of the seven children was 12 years (range 7.5-16.1) and indications included two chondrosarcomas, an osteosarcoma, a chordoma, a synovial sarcoma, a rhabdomyosarcoma, and a desmoid tumour. Tumour sites ranged from the upper cranium to the mid-to-lower abdomen. Between 1 to 3 fields were used for the proton plans, and 9, equally spaced, coplanar fields were calculated for all IMRT plans. The total integral dose delivered to the patients by the IMRT plans was predicted to be between 1.5 to 6.1 (mean 3.5) times higher than that for the corresponding proton plans. For selected organs at risk, such as the kidney, spinal cord or brainstem/medulla, the mean doses were between 2.7 to 14.3 (mean 6.4) times higher with IMRT than with the proton plans.

Conclusions: The use of protons has been found to reduce significantly the dose load to OARs and all non-target tissues compared to IMRT. However, IMRT can result in similar levels of high dose conformation. Nevertheless, in paediatric radiotherapy, the reduction of both low and medium dose level could be an important factor in minimizing the risk for secondary cancer and organ deficiencies in young children.

Phase I/Clinical pharmacology

542 POSTER

A multicenter, randomized phase III study on neurotoxicity, safety and efficacy of weekly Paclitaxel infused over 1-h vs. 3-h in patients with advanced solid tumors*

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Background: In weekly regimens of Paclitaxel (PAC) the shortening of infusion times to 1-3 hours has lead to a reduction of hematologic toxicity. As neurotoxicity is a frequently observed and often dose-limiting toxicity of PAC we investigated the effects of short infusions on the development of a peripheral neuropathy (PNP) as the primary endpoint.

Study design: Pat. with advanced cancer of different origin (mainly breast, lung, ovary, bladder, head/neck and esophagus) were randomized to a weekly regimen of PAC (100 mg/m^2) infused over 1-h vs. 3-h. PNP was evaluated by a clinical score ranging from 0 (best) to 12 (worst). Pat. increasing with their PNP score to 4-6 (moderate PNP) received a dose reduction (DR) of 25% while those exceeding 6 (severe PNP) were excluded. Pat. with at least SD after six weeks received a second cycle. Kaplan-Meier type curves for the event that PNP score exceeded 3 were calculated. (*This trial was supported in part by investigator-initiated grants from Bristol-Myers Squibb, Munich, Germany.)

Results: Between 03/99 and 01/02 a total of 22 study centers enrolled 121 patients, of whom 92 were assessable for analysis. The probability to exceed PNP score 3 raised from 0.20 vs. 0.30 after one to 0.68 vs. 0.47 after two cycles (1-h vs. 3-h: p=0.66). Grade 3 cases of neuralgia, myalgia or athralgia were predominantly observed after 1-h infusions (22% vs. 5%). Three pat. of the 1-h group exceeded PNP score 6 and were excluded, whereas the number of performed DR was equal (20% vs. 21%). Incidence of grade 3/4 hematologic toxicities was also comparable, while 3% severe HSRs occurred exclusively within 3-h infusions. Median overall survival was longer after 3-h infusions (7.5 vs. 10.4 months; p=0.32) while median progression free survival was nearly equal (3.7 vs. 3.4 months; p=0.68). The objective response rate was 38%.

Conclusions: Although we observed a slight trend towards more neurotoxicity after 1-h infusions we could not find a significant difference in this analysis. The risk to develop a significant PNP increased continuously with therapy duration in both groups, so that it seems to be primarily a question of the cumulative dosage until every patient develops a PNP. Thus, we recommend a continuous evaluation of the PNP score to avoid treatment stops by means of early dose reductions. With respect to the heterogeneity of the tumor entities the survival times and response rates have to be interpreted with caution.

543 POSTER

Tolerability of a novel bone-seeking radionuclide - the alpha emitter radium-223 - in patients with skeletal metastases from breast and prostate cancer

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Background: Pre-clinical dosimetry and experimental therapeutic studies of the alpha emitter radium-223 ($t_{1/2}$ = 11.4 days) indicate a significant therapeutic potential against skeletal metastases.

Patients and methods: 31 patients (10 breast cancer and 21 prostate cancer patients) have been enrolled in an ongoing phase I trial. In the first part of the study 25 patients was given a single intravenous injection of radium-223 as part of a cohort dose escalating design. Cohorts of 5 patients were followed weekly for 8 weeks. Initial dose level was 37 kBq kg^{-1} b.w. increasing to 74, 130, 170 and 200 kBq kg^{-1} b.w. In the second part of the study, 2 of the patients were given a second injection, resulting in a total dose of 200 kBq kg^{-1} b.w. The tolerability of repeated dosing (100 kBq kg^{-1} b.w. X 2, six weeks interval, or 40 kBq kg^{-1} b.w. X 5, three weeks interval) were studied in 6 prostate cancer patients. The primary objective was to evaluate the safety and tolerance of the drug. Toxicity was monitored using NCI common toxicity criteria and quality of life was assessed (EORTC QLQ-C 30) for all patients. Blood clearance of radium-223 was studied in the initial 25 patients.

Results: Dose-limiting haemotoxicity was not observed in the dose escalating part of the study. Reversible myelosuppression occurred, with nadir 2-3 weeks after injection and recovery during the follow-up period. Neutropenia of maximum grade 3 occurred in 2 of the 25 patients. For thrombocytes, even at the two highest dose levels only grade 1 toxicity was observed. Few adverse events were reported, with nausea as the most frequent event (4 of 5 patients) at the highest dose level. Reversible diarrhoea, grades 1 and 2, responding well to medication, were occasionally observed in all dose groups. Several patients reported pain palliation. For all patients a decline in serum-ALP values was observed. Radium-223 was rapidly cleared from blood; after 24 hours the blood activity level was below 1% of the initial level for all dose groups. To date, no trends towards increased myelosuppression upon repeated dosing have been observed.

Conclusions: Radium-223 was well tolerated by patients with skeletal metastases. Surprisingly low haematological toxicity was observed at potentially therapeutic doses. These results justify further studies to explore the efficacy of radium-223 as a novel targeted internal radioisotope treatment.

544 POSTER

A phase I trial of the novel nucleoside analog osi-7836 given on days 1 and 8 every 3 weeks: ncic ctg ind.147

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Background: OSI-7836 (4'-thio-araC) is a nucleoside analog with a number of favorable characteristics. It is inactivated by dCyd deaminase at 6-fold slower rate than gemcitabine and has prolonged intracellular activity of the active triphosphate. Antitumour effects in xenograft models were generally greater than gemcitabine at equitoxic doses and OSI-7836 toxicity was consistent with other compounds of this class.

Methods: An accelerated phase I design was used with 1-2 patients (pts) entered at each dose level until ≥ grade 2 clinically relevant toxicity was encountered, after which 3-6 pts were entered. The starting dose was 100mg/m^2 given over 30 minutes by IV infusion. Determination of dose limiting toxicity (DLT) and recommended phase II dose (RPTD) followed standard criteria.

Results: Fifteen evaluable pts have been entered to five dose levels (100, 200, 400, 500 and 600 mg/m^2) and received a total of 29 cycles, median=2 (range 1-6) to date. Demographics are as follows: F:M = 8:7, median age = 56 (range 35-75), ECOG 0:1:2 = 2:10:3, primary tumour types = colorectal [6 pts], lung and unknown primary [2 pts each], and 5 pts had other primaries. All but 1 pt had prior chemotherapy. DLTs occurred at 600 mg/m^2 and 500 mg/m^2, consisting of grade 3 fever, rash and fatigue not ameliorated despite prophylactic use of steroids, antihistamine and acetaminophen, as well as the inability to administer the Day 8 dose. Other toxicities included grade 1-2 nausea and vomiting (with adequate antiemetics), diarrhea, herpes simplex reactivation and transaminase increases. No hematological toxicity has been observed to date other than lymphopenia at all dose levels, (median nadirs 0.06 to 0.2 x 10^9/L). Pharmacokinetic analyses were performed during the course of the first dose cycle. The mean (SD) plasma half-life of the major elimination phase was 46.4 (5.28) minutes. The mean (SD) plasma clearance on Day 1 and Day 8 was 36.4 (9.36) and 40.4 (14.6) L/(hr• m^2), respectively, indicating no significant difference. OSI-7836 plasma Cmax and AUC increased with increasing dose. No objective responses have been reported, but one pt with lymphoepithelioma of the thymus showed minor tumour shrinkage of thoracic lesions.

Conclusions: DLTs consist of fever, rash and fatigue at the higher doses. The trial is currently expanding at the 400 mg/m^2 dose level to determine if this will be the RPTD for this schedule.

545 POSTER

A randomized trial of a cd-rom educational intervention for advanced cancer patients (acp) enrolling in early phase trials

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Background: Prior informed consent research for phase I trials has substantiated concerns about acp understanding of both the research purposes of early phase trials and expectations of benefit. Furthermore, few studies have developed or evaluated interventions to enhance acp understanding.

Methods: In response, we developed an interactive cd-rom for acp eligible for phase I-II trial enrollment. Using a touch-screen monitor, the cd-rom contains phase I-II trial information and videos of acp and oncologists (MDs) talking about early phase trials. To test its efficacy, we randomized acp potentially eligible for phase I-II trials to either view the cd-rom or receive a NCI clinical trials pamphlet. After consulting with a MD about phase I-II trial enrollment, subjects were then interviewed about their understanding.

Results: To date, 199 subjects have been randomized; 109 have subsequently enrolled in phase I-II trials (58% women, 88% Caucasian, 51% with college degree, 34% income >80k/yr). There are trends for cd-rom users to have both a greater understanding of the research purpose of phase I trials (37% of cd-rom users vs. 21% of pamphlet users, p=.09) and lower perceptions of the unrealistic benefit of cure (13% vs. 24%). There is a trend for cd-rom users to more often strongly agree that they were upset by the cd-rom (as compared to the NCI pamphlet15% vs. 4%, p=.19). However, 63% of cd-rom users agree their MD thought trial enrollment was a good idea (vs. 37%, p=.02) and a larger number of cd-rom users agree that its use not only changed the way they made a decision to enter a trial (28% vs. 12%, p=.02), but that it also actually changed the decision itself (20% vs. 5%, p=.06). In a subset analysis, 71% of those who completed the cd-rom subsequently enrolled in a phase I-II trial, compared to 58% who received the NCI pamphlet.

Conclusion: While the cd-rom intervention may challenge acp decisions and produce some discomfort, it has the potential to improve consent outcomes, reduce unrealistic expectations of benefit, and improve phase I-II trial accrual.

546 POSTER

A Phase I dose-escalation trial of ZD6126 administered as 5 daily doses every 3 weeks to patients with cancer refractory to other treatments

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Background: ZD6126 is a novel vascular-targeting agent that causes disruption of the tubulin cytoskeleton of rapidly proliferating endothelial cells in tumour vasculature. In vivo, these changes have been shown to lead to tumour endothelial cell detachment, resulting in vessel occlusion and extensive tumour necrosis.

Methods: A Phase I, open-label, dose-escalation study in patients with solid tumours refractory to other treatments has been conducted to evaluate the safety and pharmacokinetics of ZD6126 administered as 5 consecutive daily doses every 3 weeks. Patients were required to have a WHO performance status of 0–2 and a life expectancy of ≥12 weeks; those with significant cardiac, haematopoietic, hepatic or renal dysfunction were excluded. Subjects received ZD6126 (1 or 4 mg/m2, given as a 10-minute infusion) daily for 5 days. Cycles were repeated every 21 days until an adverse event, disease progression or other criterion warranted withdrawal.

Results: A total of thirteen patients (7 male, 6 female; mean age 52.5 years) have received ZD6126 therapy in this study (1 mg/m2, N = 7; 4 mg/m2, N = 6). Maximum concentrations of the active species (ZD6126 phenol) were observed 10–20 minutes from the start of infusion, and decayed in a bi-exponential manner with a relatively short half-life (1.01–4.26 hours on day 1; 0.78–2.45 hours on day 5). Cmax and AUC increased with dose, with no evidence of differences between exposure on day 1 and day 5. The most common adverse events were fatigue (N=7), nausea and vomiting (N=7), fever (N=5), dyspnoea (N=5), constipation (N=4), and headache (N=4). Three CTC grade 3 events were seen in patients receiving 1 mg/m2 (1 case each of hyponatraemia, peripheral motor neuropathy [not considered to be treatment-related] and intestinal obstruction, in 3 separate patients). One CTC grade 3 event (increased liver enzymes) was seen in the 4 mg/m2 group. Dose-limiting toxicities were seen in 2 patients receiving ZD6126 4 mg/m2 (1 case of increased aspartate aminotransferase and 1 case of prolonged QTc interval, although this patient also received 2 other treatments known to be associated with QT prolongation during the trial).

Conclusions: This study has provided preliminary pharmacokinetic and safety data and constitutes one of three Phase I studies designed to identify the optimal administration schedule and dose of ZD6126 for future clinical assessment.

547 POSTER

KOS-862 (Epothilone D): Phase 1 dose escalating and pharmacokinetic (PK) study in patients (Pts) with Advanced malignancies

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Background: KOS-862 (Epothilone D; 12,13 desoxyepothilone B) is a naturally occurring cytotoxic macrolide that stabilizes microtubules and induces