pre-operative chemotherapy (CT), for so called standard risk (SR) and high-risk (HR) HB, respectively. SR-HB was defined as tumour confined to the liver, involving at the most 3 hepatic sectors, and HR-HB as tumour extending to all 4 sectors and/or with intra-abdominal and/or distant extrahepatic disease.

Material and methods: SR-HB patients were treated with Cisplatin (CDDP) alone (80mg/m2 in 24hours continuous infusion -c.i.-) every 14 days X four, delayed surgery, then two more courses of CDDP. HR-HB patients were given CDDP(as above) alternating every 14 days with carboplatin (500mg/m2) and doxorubicin (60mg/m2 48hour c.i.). Three CDDP and four carboplatin/doxorubicin were given pre surgery and two carboplatin/doxorubicin and one CDDP post operatively.

Results: 77 LR and 58 HR-HB, registered from 10/1995 to 5/1998 are evaluable. 67 LR and all HR-HB were treated according to protocol. The epidemiological patients characteristics were as expected. Treatment outcome: positive RR RsR* 3-years PFS 3-years OS SR-HB 90% (80-96%) 96% (87-99%) 0.89 (0.11) 0.91 (0.07) HR-HB 78% (65-87%) 67% (54-79%) 0.48 (0.13) 0.53 (0.13) *Including liver transplantation. Time interval between courses, dose reduction, hospitalisation; organ and haematological toxicity analyses supported the finding of treatment feasibility (data not shown). No toxic deaths were reported but 2 HR and 2 SR died post-operatively.

Conclusions: Single agent CDDP and surgery seem to be effective for SR-HB treatment; despite therapy intensification, the survival data of HR-HB are only on the 50% range; short-term toxicity of SIOPEL2 regimens is acceptable. The question of CDDP-alone effectiveness is presently addressed by a prospective controlled trial (SIOPEL3)

718 ORAL

Treatment results in high risk hepatoblastoma: analysis of prognostic factors. Results from SIOPEL 2 and 3 trials.

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Background: HR-HB patients are a heterogeneous group comprising of at least 4 subgroups: patients with local disease involving all four liver sectors (PRETEXT IV), pts. with extra-hepatic intra-abdominal disease, pts. with distant metastases and pts. with low AFP (<100 ug/L). The SIOPEL 2 and 3 international trials were conducted consecutively to test efficacy and toxicity of a new chemotherapy regimen given for these patients pre- and postoperatively.

Material and methods: Patients were given Cisplatin (80mg/m^2/24hour) alternating every 14 days with Carboplatin (500mg/m^2) and Doxorubicin (60mg/m^2/48 hour). In SIOPEL 3 four Cisplatin and three Carbo/Doxo courses were given pre-surgery and 1 and 2, respectively, post-operatively. In Siopel 2 only 3 Cisplatin courses were administered pre-surgery.

Results: Between 1994 and 2001, the SIOPEL 2 and 3 trials included 131 evaluable HR-HB patients from 21 different countries (60% male, age median 19 months range 0-14 years). Fourty-seven patients had PRETEXT IV disease, 38 had metastases and 20 both. Twenty patients had AFP<100ug/L. Partial response rate to pre-operative chemotherapy was 70%. Fifty-six patients (43%) achieved a complete macroscopic resection by partial hepatectomy. Eighteen children had complete hepatectomy followed by orthotopic liver transplantation. At 1.5 years the EFS was 54% (95%CI:45%-63%) and the OS was 62% (95%CI:53%-71%). AFP<100ug/L was associated with significantly shorter OS and EFS (p<0.0001). This is in line with a significantly lower response rate to pre-surgery chemotherapy in such patients. Metastatic disease was borderline associated with worse OS (p=0.05). No other patient characteristics were identified as prognostic factors.

Conclusions: Overall treatment results in HR-HB remain un satisfactory. The failure pattern suggests that patients could benefit from an intensified pre-operative chemotherapy regime. Chemotherapy for low AFP patients should be revised. A new treatment strategy for HR-HB patients with intensified use of Cisplatin is in preparation (SIOPEL 4).

719 ORAL

Hepatocellular carcinoma in children - results of the second prospective study of the international Society of Paediatric Oncology (SIOP) - siopel-2.

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Introduction: Hepatocellular carcinoma (HCC) is the second most common pediatric malignant liver neoplasm (after hepatoblastoma - HB).

Objectives: To collect information on: biology, patients' characteristics, outcome and prognosis of pediatric HCC and compare it with HB experience.

Material: Twenty one patients diagnosed with hepatocellular carcinoma (HCC) were registered in the SIOPEL 2 study from 03.1994 to 05.1998 (17 were further analyzed). Metastases at diagnosis occurred in 18% children. Extrahepatic tumor extension and/or vascular invasion were found in 35% of patients. Multifocal tumors prevailed (53%). One patient died 17 days after diagnosis from massive GI bleeding, and never received treatment. Thirteen of the 16 treated patients received preoperative chemotherapy (SuperPLADO cisplatin / carboplatin and doxorubicin).

Results: Partial response to preop.CHT was observed in 6/13 cases (46%). Tumor resection was achieved in 8 patients (47%) (including 1 liver transplantation). Three of them underwent primary tumor excision. Six of the 8 operated pts received between 2 and 10 courses of postoperative chemotherapy. Nine cases (53%) never became operable. One patient was lost to follow-up just before planned surgery. Four of the resected patients were alive at a median follow up time of 53 months (35 to 73). Twelve pts. died due to progressive disease, one from surgical complications. The overall treatment results of HCC patients remain extremely poor (22% survival). These results show no improvement over the previous SIOPEL 1 study, in which the overall survival at 5 yrs was 28%, while event free survival was 17%.

Conclusions: 1. Survival for pediatric hepatocellular carcinoma patients remains significantly inferior to that for hepatoblastoma. Complete tumor excision remains the only realistic chance of cure. 2. Intensification of standard chemotherapy has not improved the patients' prognosis. 3. A new treatment approach is needed to increase HCC cure rate.

720 ORAL

Indefinite radiotherapy of anaplastic ependymomas and supratentorial PNET in babies and infants: results of the German HIT-SKK 87 and 92 trials.

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Background: For infants and babies intensive chemotherapy was introduced in trials to delay or omit radiotherapy. We evaluate the outcome of infants and babies with supratentorial (st) PNET and anaplastic ependymoma after intensive postoperative chemotherapy and indefinite radiotherapy, and we identify factors predictive for survival.

Materials and methods: Since 1987 in Germany and Austria infants and babies with malignant brain tumours were enrolled in the HIT-SKK 87 trial. After surgery low risk patients received a maintenance chemotherapy consisting of PROC/VCR, MTX/VCR. In high risk patients PROC, IFO/VP-16, MTX, DDP/Ara-C was followed by maintenance chemotherapy until delayed radiotherapy. In the following HIT-SKK 92 the agents MTX/VCR/CPM, MTX/VCR, MTX/Carbo/VP-16 were applied. In children with complete response the therapy was finished. In case of tumour persistence salvage chemotherapy was added. Radiotherapy was administered only in non-responders.

Results: All children received chemotherapy. 29 children with st PNET were eligible (age 3.0 – 37.0 months); 3-years OS and PFS rates were 17.2% and 14.9%, respectively. The only significant predictive factor for both OS and PFS was the administration of radiotherapy. 34 patients with ependymomas were analysed (age 1.0-33.0 months); 3-years OS and PFS rates were 55.9% and 27.3% respectively. All failures occurred with local involvement. Positive impact on survival was observed in higher age, M-stage, complete resection, and applied radiotherapy.

Conclusions: In younger children delayed radiotherapy is reasonable to spare late effects. Omission of radiotherapy jeopardizes survival, even if intensive chemotherapy has been applied. Outcome of infants and babies

with st PNET is unsatisfactory, and intensification of therapy is needed. In ependymomas the predominant site of failure is the primary tumour site. The irradiation of neuraxis did not improve survival. For ependymomas intensified local therapy is warrantable.

721 ORAL

Risk of second primary cancer in hereditary and non-hereditary retinoblastoma: results from a population based study with more than 40 years follow-up

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Purpose: To determine the risk of second primary cancer in retinoblastoma survivors, we have identified and followed the 240 patients diagnosed with the disease in Denmark between 1943 and 1995.

Methods: Data on treatment, heredity, mortality and observed/expected numbers of second primary cancers have been extracted from the Danish Cancer Registry, primary records from the clinical departments, the Danish Population Registry, and church records. Data on heredity are based on family history and genetic analysis. Median follow-up of the 210 retinoblastoma survivors is 25.2 years of age.

Results: At 40 years of age, the cumulative incidence (3%) and mortality (3%) of second primary cancer in the non-hereditary group (144 patients) is similar to the population at large. In contrast, the corresponding values for the hereditary group (96 patients) is significantly higher at 19% and 11%, respectively. Among the hereditary patients, the increased risk is the same for patients treated with or without radiation therapy for their primary disease. None of the patients have received chemotherapy. Except for a higher incidence (particularly of malignant melanomas), the second primary cancers are of the same type as the time- and age-specific cancers observed in the population.

Conclusions: Associated with hereditary retinoblastoma is an increased risk for second primary cancer. This is not linked to the use of radiation therapy but strictly to the genetic status of the patient

722 ORAL

Detection of relapse in childhood solid tumours

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Aims: Frequent follow-up, often with regular investigation, is a routine part of Paediatric Oncology. Many treatment protocols specify both the type and frequency of the investigations to be performed. There is however, little evidence as to the value of such surveillance in the detection of relapse. We thus conducted a retrospective study of relapse detection in a patient cohort.

Methods: A cohort of 316 children diagnosed with solid tumours between 1992 and 1996 was identified. This patient group had a minimum follow up period of 5 years from the end of treatment. Case notes were reviewed and numbers of clinic visits and surveillance investigations recorded. For any relapse that occurred the method of relapse detection was noted.

Results: The average age of the cohort was 5.4 years, and the mean period of follow-up was 5.9 years. 76 patients were excluded because they never achieved remission, or were lost to follow-up. 3417 routine clinic visits were made by this cohort. The frequency of clinic attendance varied from 11 visits/ patient/yr for those with bone tumours, to 6/yr per brain tumour patient in the first year after finishing treatment, although there was less variation in subsequent years. 1860 radiological investigations were performed on this patient group over this period. 60% of these were chest radiographs, 14% were ultrasounds, and 12% were MRI scans. Wilm's tumour patients had on average 11 radiological investigations/yr during this period of follow up, whilst brain tumour patients had only 3/yr. 37 relapses were detected in this cohort. 53% were detected symptomatically, 13% at routine clinic visits, and 27.5% on routine investigation. 81% of relapses occurred >1 year from the end of treatment. We calculated that routine MRI scan detected 1 unsuspected relapse for each 42 scans performed. Routine CT scan detected 1 relapse for every 129 scans performed, whilst routine chest radiography detected only 1 relapse for every 257 films. The low incidence of relapse detection by routine surveillance in this cohort raises questions as to the usefulness of such follow-up in children with solid tumours.

723 ORAL

CPMP guidance in paediatric oncology

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Background: Since 1990, the Committee for Proprietary Medicinal Products (CPMP) anticancer guideline has provided advice on the clinical investigation of anticancer agents, in particular of cytotoxic/cytostatic agents (Note for Guidance on Evaluation of Anticancer Medicinal Products in Man, CPMP/EWP/205/95). Recently, the CPMP has been working together with European paediatric oncology research groups, including the EORTC Children's Leukaemia Group, the Société Française d'Oncologie Pédiatrique (SFOP), the United Kingdom Children's Cancer Study Group (UKCCSG), the German Society of Paediatric Oncology and Haematology (GPOH), and experts from other European institutions, to produce specific guidance on paediatric oncology, with recommendations for regulatory submission, and phase I trial methodology.

Results: Promising new agents should be studied or made available to researchers, so as to avoid unnecessary delays in paediatric development. Prioritisation of agents for evaluation in children is critical. Factors to be considered include evidence of activity in pre-clinical models, mechanism of action, drug-resistance profile and activity observed in adults. It is recommended that a marketing authorisation application for anticancer agents for adult use should contain information on any past, ongoing or planned paediatric oncology development. A comprehensive overview of any pre-clinical testing in model systems of paediatric tumours should be provided. Data requirements and the timing of paediatric development should be discussed with the regulatory authorities. Sponsors should seek the advice of established international paediatric oncology co-operative groups, and regulatory authorities, early enough during the development so that agreed priorities can be followed, avoiding unnecessary delays. The existing consensus on the design of phase I trials (Smith, M., M. Bernstein, et al., (1998) "Conduct of Phase I trials in Children With Cancer." J Clin Oncol 16(3): 966-78) has also been reflected in the guideline.

Conclusions: Co-operation between the pharmaceutical industry, research groups, and health authorities worldwide can ensure a coherent approach to paediatric drug development in oncology. The paediatric addendum to the CPMP anticancer guideline can be consulted on the EMEA website (htpp://www.emea.eu.int). Finalisation is expected before the end of 2003.

724 ORAL

Caring for survivors of childhood cancers: the size of the problem

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Background: Survival for children with cancer has improved greatly, although many survivors have significant health problems from their illness or treatment, requiring long-term medical care. This study utilises survival and clinical data to estimate current and future numbers of long-term survivors and their disabilities, and considers how their care might be provided.

Materials & Methods: The West Midlands Regional Children's Tumour Registry provided data on 5,016 children aged 0-14 years diagnosed with cancer (or benign brain/CNS tumours) between 1960 and 1999. Future numbers of long-term survivors were estimated from actuarial survival rates. Treatment and late effects data were collected from their medical casenotes