ded tissues stained with HE, and for FN expression on cryostat sections. We used the MoAb antiFN from Boehringer-Mannheim. SBC (Boehringer-Mannheim) was used for immunohistochemical staining. Hematoxilin was used for nuclear staining.

Results: The expression of fibronectin is heterogenous at both benign and malignant lesions. We evaluated as negative, positive and strong positive the staining for fibronectin.

Conclusion: These results bring the fibronectin expression at a new level-that of malignancy marker. It also have the quality to reveal the perivascular metastatic capacity. We consider that the fibronectin through it's receptor property in cell adhesion can become an useful indicator for metastatic potential of the tumor and also for the tumoral evolution.

393 PUBLICATION

Dominant properties for the suppression of development of preneoplastic foci in the liver of carcinogen resistant inbred DRH strain rats

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Purpose: The post-initiation stage of hepato-carcinogenesis was investigated in carcinogen resistant inbred DRH rats and the parental Donryu rats.

Methods: Male rats (5 W) were treated with DEN followed by 3'-methyl-DAB and partial hepatectomy. At 8 weeks after the start of treatment, the number and size of glutathione S-transferase (GST-P) positive lesions were determined.

Results: The mean area occupied by GST-P positive lesions was 30% in Donryu rats but less than 4% in DRH rats despite of the presence of comparable numbers of foci in livers of both strains. This genetic property was dominantly inherited in the F1 rats by crosses of DRH and carcinogen sensitive inbred F344 rats.

Cancer in children

394 ORAL

The standards, options and recommendations (SOR) project for the management of childhood cancer

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Objectives: The "Standards, Options and Recommendations" (SOR) project, was started in 1993, and is a collaboration between the Federation of the French Cancer Centres (FNCLCC), the 20 French Cancer Centres end specialists from French Public Universities, General Hospitals and Private Clinics. For pediatic cancer, this project is a collaboration between the FNCLCC end the French Society of Pediatric Oncology (SFOP). The main objective is the development of clinical practice guidelines to improve the quality of health care and outcomes for cancer patients. The methodology is based on literature review and critical appraisal by a multidisciplinary group of experts, with feedback from specialists in cancer care delivery.

Methods: Data have been Identified by literature search using Medline and personal references lists. The main criteria considered were incidence, risk factors, prognostic factors and efficacy of cancer treatment. Once the guideline, was defined, the documents were submitted for review to national and International Independent reviewers, and to the medical committees of the French Cancer Centres which have expertise in pediatric cancer management, for agreement.

Results: To date, SOR documents have been produced for neuroblastoma, rhabdomyosarcoma, medulloblastoma, osteosarcoma and pain management in children. These recommend standard diagnostic and therapeutic approaches on the basis of file strength of published evidence. The SOR guidelines for rhabdomyosarcoma in which imaging, pathological studies, surgery, radiotherapy and chemotherapy strategies are critically reviewed, the details of SOR methodology and the planned methods of dissemination will be presented.

395 ORAL

Prognostic value of blasts on day 15 in bone marrow and of molecular evaluation of remission in children with acute lymphoblastic leukemia

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Childhood acute lymphoblastic leukemia is curable in approximately 70% of all patients with current treatment protocols. Risk-directed protocol strategies using multiagent chemotherapy have resulted in complete remission rates of 98% after induction therapy. Despite these achievements, still 25 to 30% of these children will subsequently relapse. With conventional prognostic factors at diagnosis and prednisone poor response one third of patients, who will suffer a relapse can be detected. In vivo response to multiple agent therapy appears to be an independent predictor of outcome. In this study we have evaluated the prognostic significance of early response to induction therapy, as measured by the percentage of lymphoblasts in the day 15 bone marrow aspirate and by the detection of MRD by molecular methods using clone-specific immunoglobulin and T cell receptor gene rearrangements in 75 children with ALL treated according to current BFM protocols. All children achieved morphological remission after induction chemotherapy. After a median observation time of 4.5 years (range 1–7 years) 14 children relapsed. Results of blasts on day 15: M1: 47 patients, M2: 18 children, and M3: 10 children. Five, 4, and 5 relapses occurred in the M1, M2, and M3 group, respectively. Results of MRD analysis (combined evaluation after induction and consolidation treatment): MRD low risk group 38 children, no relapse; MRD medium risk group 31 patients with 10 relapses; MRD high risk group 6 patients with 4 relapses. Log rank test showed significant differences for event free survival (RFS) between BFM risk groups ($p = 0.0039$), for M1, M2 and M3 on day 15 ($p = 0.0014$) and for MRD risk groups ($p = 0.0001$). In a stratified log rank test combining BFM risk groups and MRD groups, blasts on day 15 are not predictive for EFS ($p = 0.28$).

396 ORAL

Monitoring and functional characterization of rare tumor cells in the haematopoietic system

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The detection and quantification of rare tumor cells in the bone marrow (BM) or peripheral blood (PB) is becoming of particular significance for the treatment of cancer patients. Moreover, exact genetic and functional data of the infiltrating tumor cells can further help to better understand the biology of the infiltrating cells and thus help to refine the anti-tumor therapy in individual patients. A fully automated scanning system was adapted, to enable a sequential demonstration of tumor specific immunological and molecular cytogenetic investigations at a single tumor cell level. 200 BM samples from 60 pediatric cancer patients were analyzed sequentially using a tumor specific antigen and by demonstrating the tumor typical genetic aberration. The proliferative capacity of tumor cells was assessed by a simultaneous detection of the tumor specific antigen and the proliferation marker Ki67. Automatic analysis of 29 BM samples revealed Ki67 antigen expression in up to 78% of the tumor cells in the BM of newly diagnosed patients. A similar percentage of Ki67 positive cells was found in patients undergoing cytotoxic treatment. Automatic search and sequential genetic and immunological characterization of tumor cells prove to be a powerful diagnostic tool in clinical oncology and allow new insights in the biological nature of rare tumor cells circulating in the haematopoietic system.

397 ORAL

Cutaneoes and subcutaneous Ewing's sarcoma – A relatively indolent disease

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To analyze the outcomes of extraosseous Ewing's Sarcoma (ES) in a primary cutaneous or subcutaneous site.

Between July 1985 and March 1997, 14 patients with cutaneous or subcutaneous ES were treated.

13 had definitive surgical resections and 1 had biopsy of the mass at the time of referral. All patients received chemotherapy. Twelve patients on ES-87 and ES-92 protocols received radiation (36 Gy) to the operative bed

(150–180 cGy/fraction/day). Post-operative radiotherapy was omitted for 2 patients on POG-9354 who had complete resection of the primary tumors.

No patients had metastatic disease at presentation. 13 patients had gross total resection of the primary tumors prior to enrollment on chemotherapy. Surgical margins were negative (10), microscopic (2), and indeterminate (1). The patient who had biopsy only received induction chemotherapy followed by definitive surgical resection and post-operative local radiotherapy.

The median follow-up was 77 months (range 17–111 months). None of the patients developed local recurrence or distant metastasis. Five patients developed treatment-related sequelae.

Cutaneous and subcutaneous ES are associated with an indolent course and a favorable prognosis with multimodality treatment. The hypothesis that complete wide excision resulting in adequate local control without the use of post-operative radiation is being tested in the POG-9354 protocol to eliminate the potential risk of radiation-induced toxicity. The next goal is to tailor treatment to minimize toxicity while maintaining a high cure rate.

398 ORAL

Recommended age for total thyroidectomy in children with MEN-2a syndrome

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Introduction: Since the introduction of RET proto-oncogene as the disease related gene in MEN-2a syndrome total thyroidectomy is usually performed at an age of 4 to 5 year. Up to that time an abnormal calcitonin stimulation test in children of an affected parent was the indication for thyroidectomy. The risk of surgical treatment in these young children is scarce in the literature. Therefore we evaluated our experience and results of management.

Patients and Methods: Since 1989, eight children from MEN-2a parents with an abnormal pentagastrin test and/or proven mutated RET gene underwent a total thyroidectomy.

Results: In seven children with an abnormal pentagastrin test and in one patient with a possible abnormal pentagastrin test total thyroidectomy was performed at the age of 14, 11, 11, 10, 7, 5, and 4 years. Microscopic examination showed C-cell hyperplasia in two patients (10 and 7 yr), C-cell hyperplasia with in situ carcinoma in three pts (12, 5, 4 yr) and invasive carcinoma in the remainig two children (14, 11 yr). One of these last children (14 yr) also had nodal metastases. The recurrent nerve function after surgery was normal in all patients. One patient (11 yr) developed a hypoparathyroidism after dissection of the central region

Conclusion: Medullairy thyroid cancer can be found at an early age of 4 years in children of parents with MEN-2a. The recommended age for starting diagnostic test (RET proto-oncogen mutation) is 4 year and even at that age total thyroidectomy seems to be a save procedure.

399 ORAL

Second malignant neoplasms (SMNs) in retinoblastoma (RB)

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Genetic alterations in RB may predispose patients to the development of secondary malignant neoplasms. Overall survival and the development o SMNs was determined for RB cases identified from the SEER Cancer Incidence Public-Use Database 1973–1994. Out of 457 cases, 326 (71%) were unilateral, 121 (27%) were bilateral, and 10 (2%) were unknown. Results showed actuarial survival to be superior for unilateral versus bilateral RB ($p < 0.01$) with 15 year survival of 92% versus 70%. Approximately half of this difference could be attributed to excess deaths from SMNs. At fifteen years the risk for developing an SMN in unilateral versus bilateral RB was 0.6% versus 15.8%, respectively ($p < 0.01$). Eight out of nine SMNs had received radiation therapy (RT) and four tumors could be considered in the field of RT. The standardized incidence ratio for developing an SMN in bilateral RB was 565. Germline deletion or mutation of the RB gene appears to confer increased susceptibility to neoplastic transformation. Surveillance for SMNs in bilateral RB is warranted.

Years	Unilateral No. at Risk	% SMN (SE)	Bilateral No. at Risk	% SMN (SE)
0	326	0 (0)	121	0 (0)
5	181	0 (0)	60	2.1 (1.5)
10	122	0.6 (0.6)	34	4.6 (2.6)
15	68	0.6 (0.6)	17	15.8 (6.8)
20	15	0.6 (0.6)	4	45.8 (18.2)

SE = Standard Error.

400 ORAL

Early prophylactic treatment with high-dose recombinant human erythropoetin (rHuEPO) in children with solid tumors

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Purpose: Children with solid tumors who are treated with chemotherapy (CT) frequently develop anemia and may need to be transfused. Avoidance of transfusion is the goal in pediatric cancer patients and rHuEPO has been shown to be effective in ameliorating anemia in adult solid tumor cancer patients on CT. A pilot study to assess the benefit of rHuEPO as prophylaxis for anemia in children with solid tumors was designed.

Methods: In an open, nonrandomized trial we studied 41 children, median age 13.5 years (range 5 months–26 years), with solid tumors (osteosarcoma: 44%; Ewing's sarcoma: 24.4%; rhabdomyosarcoma: 12.2%; others: 19.4%) and CT-induced anemia. Treatment with rHuEPO (Erypo® (epoetin alfa), Janssen-Cilag, Austria) was started during the first course of CT before anemia was observed. The patients received 150 international units (IU)/kg rHuEPO 3 times weekly if the hemoglobin value was 12 g/dL or greater, and 300 IU/kg if the hemoglobin value was 12 g/dL or less. All patients received oral iron supplementation. During the study, rHuEPO responders did not receive packed red blood cell (RBC) transfusion in any 2-week time period, while a non-responder was defined as a person who received packed RBCs during 2 consecutive weeks. Such patients were therefore excluded from further receiving rHuEPO.

Results: The median observation time was 6 months (range 1-11 months). 36/41 (88%) patients were responders to rHuEPO; 16/41 (39%) did not receive packed red blood cells at any time during the course of chemotherapy. 25/41 (61%) received a median of 3 units of packed red blood cells (range 1–15 units).

Conclusion: In our study, early prophylactic treatment with high-dose rHuEPO seems to have a major benefit to prevent CT-induced anemia in children with solid tumors. Therefore, we suggest that a randomized study with rHuEPO in children with solid tumors should be initiated.

401 POSTER

Results of first multicentric studies of therapy children and adolescents with acute lymphoblastic leukemia in Ukraine

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Purpose: General level of pediatric oncology-hematology in post-sovjet countries was extremely low only some years ago. Introduction of modern treatment strategy for the most frequent oncologic disease in childhood (ALL) in frame of controlled multicentric study was used for achieving progress in this field.

Methods: In 1993 6 (later on 8) pediatric hematologic centers in Ukraine organized Cooperative Group of Pediatric Leukemias and Lymphomas (GPLLU). 117 pts were enrolled in the first prospective ALL-GPLLU-93 Study which was based on Protocol ALL-BFM-90 with some modifications (1 g/m^2 MTX instead of 5 g/m^2); 275 pts were included into the second ALL-GPLLU-95 Study (with ALL-BFM-95 stratification for Risk Group) till 1.01.99.

Results: I first Study 5-years pEFS was 0.68 (SD = 0.06) with pS = 0.72 (SD = 0.06); in second Study pEFS for 43 month was 0.78 (SD = 0.07) with pS = 0.79 (SD = 0.05). The incidence of Early Deaths (1.8% vs 3.4%) and Deaths in remission (4.7% vs 7.7%) markedly decreased in second Study comparatively to the first one.

Conclusions: Introducing of modern therapeutical strategy in frame of controlled cooperative Studies resulted in dramatic improvement in outcome of patients with ALL and therapy results became compatible with data of analogous western Studies. At the same time cooperation between different oncohematologic centers helps them in achieving fast professional development.