35.

HALF-BODY IRRADIATION (HBI) IN THE TREATMENT OF METASTATIC EWING'S SARCOMA RESISTENT TO CHEMOTHERAPY. M.Gasparini, F.Lombardi, A.Lattuada, F.Fossati-Bellani, C.Gianni. Istituto Nazionale per lo Studio e la Cura dei Tumori, 20133 Milan, Italy.

Upper and lower HBI in two subsequent sessions were delivered to 21 consecutive patients with disseminated Ewing's sarcoma relapsing after or while on radiotherapy and multidrug chemotherapy. A 6 MeV linear accelerator was utilized to deliver a midplane dose of 6 Gy in one single fraction. The interval between the two sessions varied according to the degree of myelosuppression, ranging from 4 to 8 weeks. The median age of patients was 16 years (range 8 to 47 years). Sites of metastatic deposits before HBI were as follows: multiple skeletal lesions (8 patients), multiple pulmonary metastases (7), one single bone lesion (4), disseminated bone and lung metastases (2). Thirteen of 21 patients (62%) received both sessions of radiotherapy. Only one session of HBI, either upper or lower, was given to 6 and 2 patients, respectively. Seventeen sessions were performed to treat painful metastases. A complete pain control was obtained in 15 cases (88%). This lasted for 2 to more than 17 months. Twenty-five of the 34 total sessions of HBI were employed to treat overt metastases. The overall response rate was 43%. At the time of the present analysis, 7 of 21 patients (33%) are alive 7 to 36 months from their first HBI session. Three patients are free from progressive disease. Besides a transient pneumonitis, which cleared after steroid therapy, no major or fatal complications were recorded. HBI resulted to be mostly effective in patients relapsing while off chemotherapy with metastases confined to the lungs or to one single bone segment. This is an ongoing clinical trial.

36.

TREATMENT BY SEQUENTIAL RADIOCHEMOTHERAPY OF SOFT TISSUE SARCOMA. RADIOBIOLOGICAL BASES AND PRELIMINARY CLINICAL RESULTS. C. Dionet, F. Deméocq. Centre Jean Perrin, Place Henri Dunant, 63011 Clermont-Ferrand Cédex, France

Based on cellular kinetics data obtained by monolayer cell culture, we have shown, on L1210 ascitic tumour in the mouse, the potentialisation of X-rays and of the chemotherapic association of 5-Fluorouracil (5-Fu) and cis-platinum (cis-DDP). We have developped a sequential treatment that can be applied in human therapy, and which has given us encouraging results in soft tissue sarcoma. The aim of the protocol is to treat, with a minimum of side effects, lesions that have resisted normal therapy. It is applied to patients who have never been treated with large doses of cis-platinum. The treatment takes place over 7 days and consists of : D_1 to D_7 : 5-Fu at 370 mg/m^2 ; D_1 and D_2, then from D_5 to D_7 : cis-platinum 15 mg/m^2 ; D_3 and D_4 : X-rays, total dose 8 to 10 Grays depending on the extent and position of the lesions. 5-Fu is used as inhibitor of X-ray potential lethal damages (PLD) repair, and as potentialisor of cis-platinum (own work). Cis-DDP administered over several days is as effective as a single, large dose (own work). The choice of D_3 and D_4 for administration of X-rays allows maximum benefit of potentialisation of X-rays by cis-DDP and of that of cis-DDP by X-rays. This treatment is repeated after a rest period of 3 weeks. Disadvantages are cumulative dose of cis-DDP and long-term thrombopaenia. Advantages are the practicability, which is the same as for sequential chemotherapy, and the tolerance, which is usually good both from the haematological and clinical points of view. The results are still in their preliminary stages, but we have always obtained a good response on soft tissue sarcoma : on pulmonary metastasis of synovial sarcoma, volume reduction was at least 80 % after 3 cycles ; an inoperable malignant abdominal schwannoma became, after 4 cycles, an entirely necrotic, operable mass ; a pelvic leiomyosarcoma disappeared after 5 cycles. We are currently treating other cases, but it would be premature to discuss them at the moment. The encouraging results incite us to continue this therapy, and to extend it to other lesions.

37.

CHEMORADIOTHERAPEUTIC CONSERVATIVE MANAGEMENT IN 23 PATIENTS WITH LOCALLY EXTENDED BILATERAL RETINOBLASTOMA. J.M. Zucker, N. Lemercier, P. Schlienger, E. Margulis, C. Haye. Institut Curie.

To reduce the number of enucleated eyes and to improve the useful vision in locally advanced disease, we developed a conservative approach in 23 patients (pts), 9 boys and 14 girls aged of 3 to 36 mths (median = 8 mths) with bilateral non metastatic retinoblastoma. 36/46 eyes were Reese stage V and in 10/23 pts unilateral enucleation had been mandatory at first. All pts received two courses of VAC (vincristine 1,5 mg/m2 day 1, actinomycine D 10 gammas/kg day 1 to 5, cyclophosphamide 200 mg/m2 day 1 to 5) at a three wks interval, followed by irradiation with a 22 MeV electron beam delivering 45 grays in 5 wks ; after one mth, 6 monthly courses of VAC were resumed.

Results : overall follow up is 12 to 54 mths (median = 24 mths). 2/23 pts died from neuromeningeal involvment at 18 and 22 mths. 21/23 pts are alive and well 2 to 48 mths after cessation of therapy (median = 14 mths). 5 of them are blind. 12 keep one eye, 4 keep both eyes.

. There was, on the basis of fundoscopy, a good partial response to initial chemotherapy in 9 patients, a moderate decrease of the tumor in 8, no response without progression in 6.

. Later on 15 secondary enucleations -12/15 in the first 10 months- were done in 14/23 pts due to tumor progression in 11 cases. 7/14 pts kept one useful eye which was initially staged II to V in 4 cases.

. A useful vision was kept in 12/13 eyes (11/12 stage V) of 9/23 pts (4/9 keeping both eyes).

Conclusions : 1°- These preliminary results are encouraging both in terms of visual capacity and cosmetics.
2° A careful fundoscopic supervision must be extended to detect late local relapses.

38.

MANAGEMENT OF RETINOBLASTOMA (R.B.) BY PRECISION MEGAVOLTAGE IRRADIATION. J. Schipper, K.E.W.P. Tan. Dept. of Radiotherapy Utrecht, The Netherlands.

The conservative management of R.B. in The Netherlands is centralized in Utrecht. The principal concept in the treatment of R.B. in this centre is radiation therapy (R.Th.) followed by lightcoagulation (L.C.) and/or cryotherapy (C.T.) if there is some doubt as to whether the tumour is still active. R.Th. is administered by means of a highly accurate megavoltage X-ray beam technique previously described (1). The dose of radiation is standardized at 45 Gy (4500 rad) given in 15 fractions of 3 Gy each, 3 fractions per week. Between 1971 and 1980, 31 children with R.B. have been irradiated to at least one eye. Of the 58 affected eyes, 16 were primarely enucleated, one was lightcoagulated only and 41 were irradiated. Of the 41 irradiated eyes, 27 were additionally treated by L.C. or C.T. and 7 were ultimately enucleated. The percentages of cure of the irradiated eyes with a minimum follow-up of two years were 100%(8/8), 100%(9/9), 75%(6/8), 85%(11/13), and 0%(0/3) in stages 1 to V, respectively. Twelve eyes developed a clinically detectable radiation cataract (R.C.); in 5 of these the lens was aspirated. R.C. developed exclusively in those lenses of which a major part was included in the treatment field. In a preliminary study (1) the likelihood and extent of cataract formation was found to be directly related with the dose of radiation to the germinative zone of the lens epithelium. Irradiation of a posterior portion of 1 mm of the human lens with a sharply edged irradiation beam will not produce a radiation cataract.

References: (1) Schipper, J.: Retinoblastoma. A medical and experimental study. Thesis, State University of Utrecht, 1980.

39.

INTESTINAL MICROBIAL FLORA SUPPRESSION IN PREVENTION OF INFECTIONS IN PATIENTS UNDERGOING CYTOTOXIC OR RADIATION THERAPY. F. Waldvogel, Department of Medicine, Geneva, Switzerland.

Besides tumor growth, or therapy induced destruction of the mucosal barreer, the absolute granulocyte count is one of the best predictors of bacterial or fungal infection in patients with malignancies. 50% of these infections are caused by flora, acquired subsequent to initial hospitalization. Major pathogens include S. aureus, E. coli, Klebsiella species, Pseudomonas aeruginosa, Candida species and Aspergillus species. Viruses contribute to the morbidity of these patients, but rarely to their mortality except for cytomegalovirus (bone marrow transplants). Herpes zoster/varicella virus (lymphomas), and the newly recognized gastrointestinal viruses.

Gastrointestinal bacterial and fungal suppression by non absorbable antibiotics has therefore been used extensively as a major means to prevent infections in neutropenic patients. Full suppression with large spectrum antibiotics has given contradictory results. Selective suppression with Co-trimoxazole, or partial suppression with a combination of Co-trimoxazole and an antifungal agents represents promising direction for the future. These results have to be compared to other possible means of preventing infections in granulocytopenic patients, such as reversed precautions, strict hygene, vaccinations and antisera, and new compounds decreasing the colonization with pathogenic bacteria and fungi.

40.

INFECTIONS AND OTHER TOXIC DEATHS IN THE SECOND NATIONAL WILMS' TUMOR STUDY. B.Jones, N.Breslow, J.Takashima, for the National Wilms' Tumor Committee, West Virginia

University Medical Center, Morgantown, West Virginia, United States.

In the Second National Wilms' Tumor Study there were 18 deaths unrelated to tumor recurrence. Seventeen of these were directly or indirectly attributable to the tumor therapy. Infection during periods of drug induced leukopenia resulted in seven deaths - 2 pneumonia, 3 pneumocystis and 2 gram negative sepsis. There were four instances of liver necrosis - one attributable to chemotherapy alone and three the combination of radiotherapy and chemotherapy. Of particular concern were four infants under one year of age with clinical group I or II disease who had toxic deaths. One died of pneumonia, one of pneumocystis and two of hepatic necrosis. One of the latter two was related to a single course of actinomycin D and vincristine. Five additional infants experienced severe hematologic toxicity and survived. Subsequent to these experiences the doses of all chemotherapeutic agents were reduced by 50% for infants under one year of age. After this dosage change there were no toxic deaths in this age group and only 4/57 had severe hematologic toxicity as compared to 9/47 prior to the change. An analysis of the therapeutic effect of this dose reduction showed 3/48 tumor relapses on full dose and 7/60 on half dose. The difference is not statistically significant. This is believed to be the first documented demonstration of the vulnerability of infants to standard doses of anticancer drugs whether calculated on a per square meter or a per kilogram basis.

41.

SIMULTANEOUS ADMINISTRATION OF NALIDIXIC ACID (NA) AND HIGH DOSE MELPHALAN (HDM) IN CHILDREN, CAUSING DEATH DUE TO SEVERE SIDE EFFECTS ON THE INTESTINAL TRACT. P.A.Voûte, J.van der Noordaa, C.D.M.Dobbelaar. Werkgroep Kindertumoren, Emma Kinderziekenhuis and Netherlands Cancer Institute, Spinozastraat 51, 1018 HJ Amsterdam, The Netherlands.

Oral administration of NA was used to prevent infections in 5 children with wide spread metastases of neuroblastoma. They were treated with HDM 140 mg/m^2 i.v. Oral medication of NA was started 3 to 10 days before HDM was given. NA was used in a dose of 100 mg/kg/daily, at that time no other drugs to prevent infections were given. In all five children severe blood containing diarrhee occurred 1 to 2 days after HDM treatment. All 5 patients died, 3 of them clearly due to severe intestinal toxicity. At autopsy haemorrhagic ulcerative colitis was found. In one patient intestinal necrosis was the cause of death. Two patients were treated twice with HDM. One of them the first time without NA and without intestinal problems. The other patient received the first time a low dose of NA (30 mg/kg) without intestinal problems.

Six other patients have been treated with HDM without NA and intestinal toxicity did not occur.

It is known that NA alone can cause haemorrhagic enteritis. It is a possibility that HDM potentiates the effect of NA. NA to prevent infections should be considered dangerous when used together with cancer chemotherapeutic agents. The simultaneous medication of NA with cancer chemotherapeutic alkylating agents should be avoided.

42.

CHEMOTHERAPY IN CHILDREN WITH CANCER AND SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT TO REDUCE THE RISK OF SEVERE INFECTION. J.de Kraker, P.A.Voûte, J.van der Noordaa, W.J.Terpstra, C.D.M.Dobbelaar. Werkgroep Kindertumoren, Emma Kinderziekenhuis and Netherlands Cancer Institute, Spinozastraat 51, 1018 HJ Amsterdam, The Netherlands.

27 children with different diagnoses of malignancies under heavy cancer chemotherapy became severely granulocytopenic. They were prophylactically treated following a protocol for selective decontamination of the digestive tract (SDD) which maintains the colonisation resistence. For each patient a historical control with identical disease and treatment was selected. The decontamination regimen consisted of a combination of co-trimoxazole (8 mg/kg trimethoprim, 40 mg/kg sulphamethoxazole), polymyxin E 10 mg/kg, nystatin 10^5 units/kg given in daily oral doses. Twice a week throat, nose, faeces and urine were cultured. Depending on the bacterial flora nalidixic acid or cephradine were added. Tobramycin or carbenicillin were added in case of severe clinical infection.

In 27 children with SDD and in 27 of the control group, 39 and 53 'study episodes' were analysed. A study episode was defined as an episode of at least 7 days during which the granulocyte count was < 1.0×10^9/l. In the SDD group 39 episodes were counted with a mean duration of 16.4 days; in the control group 53 episodes with a mean duration of 15.8 days. The frequency of bacteraemia in the SDD group was 3, in the control group 12. One patient in the SDD group died due to septicaemia against 6 in the control group. In our experience SDD in children under heavy cancer chemotherapy is a good method to reduce severe infections by aerobic gram negative rods, Staphylococcus aureus, yeasts and fungi. It is relatively easy to perform and can be done on an out-patient base, but it requires a well equiped bacteriological laboratory.

43.

MODULATION OF CHEMOTHERAPY INDUCED LEUKOPENIA: ROLE OF LITHIUM CARBONATE (LI) AND OXYMETHOLONE (OXY). P. Steinherz, G. Rosen, D. Miller. Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, NY, NY, U.S.A.

Amelioration of chemotherapy induced neutropenia in children by Li was demonstrated by us in a randomized study (J. Ped. 96:923) and then in a randomized, crossover study within the same patient (Li Effects on Granulopoiesis and Immune Function, Plenum Press). The degree and duration of leukopenia was reduced, not eliminated. Androgens have also been reported to reduce myelosuppression by a different mechanism. To evaluate the possible additive leukocyte count enhancing properties of Li and Oxy, patients (1-21 yrs. old) were randomized to receive Li or Li plus Oxy after chemotherapy. Seventy-one trials with Li, 63 with both drugs, and 79 in the control group were compared. White blood cell count and neutrophil nadirs were better in both treatment groups than in the control (P=0.001) but an additive effect of Oxy above and over Li alone was seen only in patients under 15 years old (P=.05). The median duration of severe neutropenia (absolute neutrophil count <1000/mm^3) was 6.2 d/pt in the control group but only 4.5 d/pt and 3.8 d/pt in the Li and Li plus Oxy groups, respectively (P=0.001). In the control group, 161 patient days were spent in the hospital for fever while neutropenic (2.1/pt), while patients were hospitalized 53 days (0.8/pt) and 29 days (0.5/pt) after Li and Li plus Oxy respectively (P=0.02). While the majority of the patients lost weight in the control and Li treatment group, the patients on Oxy gained weight (median 1.25kg) P=0.00001. Li reduces the period of neutropenia after chemotherapy during which the patients may acquire infection. The addition of Oxy does not substantially lessen myelosuppression in most patients but improves the patients' appetite and weight.

44.

TREATMENT OF SEVERE VIRAL INFECTIONS IN CHILDREN WITH MALIGNANT DISEASES. **P.Cvetković, E.Gebauer, Lj.Dimitrovska. Children's University Hospital, Belgrade and Institute for Health Protection of Mother and Child, Novi Sad, Yugoslavia.**

Severe viral and viral associated with bacterial infections frequently occur during treatment of children with malignant diseases. These infections can seriously jeopardize the results acchieved in treating the basic illness. Children with malignant diseases are defenceless against infections, particularly in the induction phase of the treatment, due to the lowered resistence caused by the basic illness and cytotoxic therapy. 24 children treated for lymphoblastic, non-lymphoblastic and chronic granulocytic leukemia, non-Hodgkin lymphoma, Wilm's tumor and neuroblastoma developed severe infections while under intensive treatment of their basic illness. Infection causes were varicella(7 patients),parotitis(5),adenovirus(6), influenza A and B (5),herpes simplex(3),rubella(4) and other unidentified viruses. These infections were mostly followed by bacterial infections. The infections were treated by antibiotics, whole blood and conc.leukocytes transfusions, as well as endobulin-immuno in doses from 500 to 11000 mg. The acchieved treatment results were satisfactory. Only one patient developed urticaria during administration of endobulin. It is concluded that endobulin is a valuable drug in the treatment of severe viral and combined infections in children with malignant diseases, particularly when there are not sufficient separated granulocytes on our disposal.
