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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.
