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Incidence of TEL/AML1 fusion genes in children with ALL: Risk assessment by BFM and MRD criteria

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Background: The fusion of TEL and AML1 genes is the most common chromosomal translocation in childhood acute lymphoblastic leukemia (ALL). The incidence of this translocation is about 25% at diagnosis and was found to be associated with an excellent prognosis. There are controverse data about the incidence at relapse in different treatment protocols. Sofar, no data have been reported on the response to chemotherapy by molecular methods (minimal resiudal disease, MRD) as one of the most powerful prognostic factors.

Aim of the Study: To analyse children with ALL at diagnosis and relapse for the incidence of TEL/AML1 and compare MRD-based risk stratification with clinical outcome.

Patients and Methods: 53 children with ALL treated according to ALL-BFM 90/95 protocols were included. TEL/AML1 translocation was analysed by FISH. Leukemia-specific antigen receptor gene rearrangements were used for MRD detection. MRD risk groups are: low risk (LR) no detectable MRD after induction, intermediate risk (IR) MRD 10-3 before consolidation, high risk (HR) "10-4 before consolidation therapy.

Results: After a median observation time of 5.7 years 13 patients suffered a relapse. At diagnosis 14 leukemias were TEL/AML1 positive. Of these 3 children suffered a systemic relapse. Children with TEL/AML1 negative ALL who relapsed remained TEL/AML1 negative.

According to BFM risk stratification 4 and 10 children with TEL/AML1 positive leukemias were treated according to BFM SRG and MRG protocols, respectively. The three relapses occurred in the MRG patients. When MRD risk stratification was applied 5, 7 and 2 children were in the MRD based SR, IR and HR group. Relapses occurred in the IR (2 patients) and HR group (1 patient).

Conclusion: The incidenc of TEL/AML1 positive leukemias is identical at diagnosis and at relapse in children treated according to ALL-BFM90/95 protocols. Children with relapse of the TEL/AML1 positive leukemia were not in the MRD-based LR group, in which no relapses occurred.

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Ex vivo purging using MC540 photoirradiation therapy enhanced by amifostine (WR 2721)

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Photodynamic treatment using MC540 as a photosensitising dye has a potential use in the purging of neoplastic cells from autologous bone marrow grafts. Aminothiols exert cytoprotection on normal tissues from systemic chemotherapy. This study was designed in order to investigate the effect of Amifostine (WR-2721) on leukemic and normal bone marrow cells after MC540 photoirradiation therapy. Bone marrow cells from children with acute leukemias (AL) at initial diagnosis and in remission under maintenance chemotherapy as well as HL-60 leukemic cell line were incubated with Amifostine (1.5 mg/ml) for 15 min and then with MC540 (20 g/ml) for 1 hour. Afterwards, they were exposed to different Argon Laser 514 nm doses. Cell suspensions which were not incubated with Amifostine were used as controls. Cell survival was estimated with trypan blue supravital stain following a 24 hour incubation and leukemic cell line has been studied in continuous cell cultures of 4 weeks duration. The survival of normal bone marrow progenitors has been estimated by colony formation assay in semisolid cultures. Our results showed that Amifostine: 1) has enhanced the photokilling effect of MC540 on both HL-60 cell line and fresh bone marrow leukemic cells 2) significantly protected bone marrow precursors from children with AL under chemotherapy from cytotoxicity induced by photodynamic treatment (39.05 + 4.11% vs 62.9 + 9.9%, p = 0.008), 3) has improved the survival of bone marrow committed progenitors (24.17 + 8.8% vs 5.67 + 1.7%, p = 0.08 for CFU-E, 76.33 + 39.14% vs 48.25 + 21.49%, p = 0.3 for CFU-GEMM and 44.69 + 11.2% vs 29.15 + 9.6%, p = 0.15 for CFU-GM). These differences were found to be statistically significant only for BFU-E (60.27 + 15.37% vs 18.82 + 4.64%, p = 0.017) colony formation. In conclusion, Amifostine (WR-2721) seems to enhance the photokilling effect of MC540 photoirradiation on leukemic cells and in addition to the above action exerts cytoprotection upon normal bone marrow cells; thus this agent could play a significant role in clinical use of MC540 mediated phototherapy.

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Radiotherapy for unresectable or marginally resectable osteosarcoma

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To assess local control following radiotherapy for unresectable osteosarcoma.

Between April 1967 and October 1997, 16 patients with osteosarcoma received radiation therapy to 19 sites. RT alone was used in 12 sites, and combined with surgery in 7. The median dose was 60 Gy (range, 27.5 to 82.8) using conventional fractionation (1.8 to 3 Gy once daily, QD) in 6 cases and hyperfractionated RT (1.1 to 1.5 Gy, twice daily, BID) in 13 cases. Response to chemotherapy (CT) among 14 treated prior to RT was progressive (PD, n = 7) or stable (SD, n = 7). Concurrent chemotherapy was delivered during 10 courses. At time of analysis, 9 of 16 patients are alive at a mediam time of 78 months.

Overall, 8 of 19 sites remained free of progression through last follow-up or death; median interval of control is 5.1 months (range, 0.2 to 355). Local tumor control has been achieved in 2 of 12 cases with RT alone (60 Gy delivered in 7), 3 of 3 with pre-operative RT and 3 of 4 with post-operative RT. Local tumor control has been maintained in 5 of 7 cases of SD with prior chemotherapy and 2 of 7 cases of PD. Six of 10 patients with concurrent CT, and 2 of 9 without CT have evidenced local control. Neither fractionation nor treatment interruptions affected outcome.

Local control of osteosarcoma with conventional RT, in absence of radical resection is a significant problem. In marginally resectable patients, adjuvant radiotherapy may improve local control. While hyperfractionated RT to 60 to 70 Gy for unresectable disease may improve normal tissue tolerance, tumor control remains poor.

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Ewing's sarcoma: A review of treatment outcomes and morbidity in patients aged 16 and less treated in British Columbia between 1980 and 1992

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Purpose: To review the outcome of treatment of Ewing's sarcoma in British Columbia for patients (pts) aged * 16 yrs after a minimum of 7 yrs follow up.

Methods: A retrospective chart review of these pts (recorded on a provincial registry) seen and treated between 1980 and 1992.

Results: There were 33 pts. Age at diagnosis ranged from 2 to 16 yrs. Median age at diagnosis was 11.5 yrs. All pts received adriamycin containing combination chemotherapy. The maximum dose of adriamycin given was 450 mg/m^2. 28 pts received XRT alone and 5 surgery alone as local therapy. The minimum follow up of these pts is 7 yrs. Average survival is 8.3 yrs. The mortality rate is 39% (13 pts). 27% (9 pts) died from recurrent disease. 1 died due to early complications related to chemotherapy, 2 died due to adriamycin induced cardiomyopathy, 1 due to chest wall deformity secondary to surgery leading to respiratory failure. Long term complications: 5 pts have left ventricular dysfunction requiring medication and 1 pt is surviving after heart transplant. 1 pt suffered spontaneous bone fracture after trivial injury within the previous XRT field. 4 pts with head and neck tumors have significant facial hypoplasia, dental decay and trismus. There have been no cases of second malignant neoplasm arising in any pts yet.

Conclusion: Long term complications in survivors of Ewing's are significant. Multidisciplinary follow up is mandatory.

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Astrocytomas of the cerebellum in children

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Purpose: To analysis the effect of postoperative radiotherapy in childhood cerebellar astrocytoma.

Methods: Between January 1978 and December 1997, 100 children (aged 17 years or younger) with astrocytoma were treated. We have retrospectively reviewed 39 patients with diagnosis of astrocytoma of the cerebellum. Of the 39 patients in this study, 22 were girls and 17 were boys. Their ages ranged from 2 to 17 years of age, with a mean of 10 years. Presenting signs and symptoms were papilledema (81%), headache