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Risk estimation of radiation-induced thyroid cancer in children undergoing prophylactic cranial irradiation with photons 6 MV – A Monte Carlo study

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Background: To estimate the risk of thyroid cancer induction resulting from prophylactic cranial irradiation in children with acute lymphoblastic leukemia.
Material and methods: The MCNP (4C2) Monte Carlo code was used to simulate a 6 MV linear accelerator photon beam (Philips/Elekta SL75/5). Mathematical anthropomorphic phantoms generated by BodyBuilder software (White Rock Science, White Rock, NM, USA) to simulate the average individuals of 3, 5, 10 and 15 years old, were used. Prophylactic cranial irradiation was modeled with two lateral and opposed fields at 100 cm source-to-skin distance. For each patient age, lead blocks shielding facial structures and eye globes, on a Lucite tray, were modeled. The mean radiation dose to thyroid gland was calculated. Additionally, a 10-cm-thick lead block on the patient couch, to protect the thyroid gland, was simulated by MCNP code and the mean radiation dose to shielded thyroid gland was determined. The risk for thyroid cancer induction was assessed using appropriate risk coefficient.
Results: The percentage thyroid dose was found to vary with respect to child age. For a child of 3, 5, 10 or 15 years old, the percentage thyroid doses were 4.4, 4.0, 3.45 and 2.85%, respectively. For a treatment course delivering 20 Gy to tumor, thyroid dose varies from 57.6 to 88.0 cGy depending on child age. The consequent excess relative risk of thyroid cancer induction was found to be 6.8, 6.2, 5.3 and 4.4 for a child of 3, 5, 10 and 15 years old, respectively. The use of a couch block reduced the thyroid dose and the consequent excess relative risk by 40 to 62%, depending on child age.
Conclusions: Prophylactic cranial irradiation in children can result in an increased risk for thyroid cancer induction. The use of the appropriate thyroid shielding can considerably reduce (40 to 62%) the risk for carcinogenesis.

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Negative prognostic factors in childhood ALL – the experience of a single Romanian center

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Background: The prognostic and evolution of ALL in children has become increasingly better during the last decade. Still, in our center, the cohort of patients submitted to standardized treatment, reached a 5 year event free survival (5yEFS) of only 52%. Observing that our results do not measure up to those found in the literature, we proceeded to analyze the causes that led to our results.
Material and method: The study was conducted on 156 patients with ALL diagnosed and treated according to BFM 1990 and 1995 in our center in the period of 1990–1998. We analyzed the demographic data: sex, ethnic group, age, clinical and biological (Hb, L, FAB type, karyotype, immunophenotype, and molecular biology) data at the onset of disease, response to treatment, and the 3 and 5 year EFS.
Results: Forty-three percent of our patients were over 6 years old, while 15.3 were under 2y.o. Male to female ratio was 1.29. Twelve percent of them belonged to the rroma ethnic group. CNS involvement at onset was present in 3.84% of patients, while mediastinal tumor was found in 0.64% of them. The onset values of leukocytes (L) and hemoglobin (Hb) were assessed as follows: 16.3% of patients had >50,000/mm^3; 5yEFS was 57% in patients with L>50,000/mm^3 and 78% in those with L<20,000/mm^3; Hb >8 g/dl was found in 34% of patients; 5yEFS was 50% in patients with Hb>10 g/dl and 75% in those with Hb<8 g/dl ($p = 0.0006$); FAB type L2 was present in 17%of patients while L3 was demonstrated in 3.2% of them. Immunophenotype T was found in 3.2% of patients; CD10 was negative in 10.5%. Quantitative cytogenetic anomalies were found in 54% patients while qualitative anomalies were present in 16%. Molecular biology (PCR) studied in 35.89% of our patients revealed rearrangements in 27% of them (MLL-AF4 – 2.56%; BCR-ABL – 1.28%). Positive response to corticosteroids influenced the overall survival, with 5yEFS of 79%, while resistance to corticotherapy led to 31% 5yEFS ($p = 0.0023$). Lack of compliance to treatment understood as exclusion of 1 drug was faced in 19.87% cases, reduction of doses in 8.97%, delay in administration of drugs in 47.43%. Stop or refusal of therapy had a deleterious impact on the long term survival in 4.48% of our patients. CNS prophylaxis was not administered in 32% of cases.
Conclusions: When compared to the literature our results are worse due to the particularities of the studied cohort: increased percent of patients older than 6 years and under 2 years of age, increased proportion of patients with FAB L3 and CALLA negative patients, hyperdiploid status in 26.3% patients. However, the most important factor for negative prognostic was lack of compliance to treatment. We presume better results in the group of patients treated during 1998–2005.

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Late effects of CNS prophylactic treatment in childhood due to ALL using Magnetic Resonance Spectroscopy (H-MRS)

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Purpose: The aim of this study was to evaluate changes in magnetic resonance imaging (MRI) and magnetic resonace spectroscopy (MRS) of the brain in survivors with ALL to assess neurotoxicity follow prophylactic treatment including cranial irradiation and/or intrathecal administration of methotrexate.
Methods: The study was performed including two groups of patients. The first group-30 children had been irradiated and received intrathecal methotrexate and second group consisted of 15 children treated with intrathecal metotrexate without radiotherapy. Radiotherapy was performed using fraction dose 1.8 Gy up to total dose of 18 Gy. MTX chemotherapy doses depended on risk group.
Results: MRI of brain was abnormal in 13(43%) cases in group with cranial irradiation and intrathecal chemotherapy. We observed significant changes in H-MRS metabolite ratios even in patients without changes on imaging. We didn't observe changes on imaging and only one child had altered metabolism observed by MRS in group of patients without radiotherapy.
Conclusions: The MRS could be a valuable method to assess brain tissue metabolism after radiotherapy. That method may be recommended for children with ALL to observe neurotoxicity of prophylactic irradiation.

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Antiangiogenic therapy in high risk medulloblastoma: the role of microarray analysis

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It is noteworthy that a characteristic of posterior fossa tumors is high level of neovascolarization. Studies showed this process is supported by bFGF, VEGF and PGE2 high level expression. A major focus in high risk medulloblastoma is identifying molecular targets, as growth factors, COX2 and microvessel density that can be used for an antiangiogenetic therapy. Expression profiling of medulloblastoma by microarray analysis can be used to identify the genes implied in neovascularization process, thereby revealing new targets for therapy.
The authors determined the molecular profiling in liquor cell samples of five medulloblastoma relapses by microarray analysis. The patients underwent surgical treatment of primary tumor followed chemotherapy before and after radiotherapy and stem cell reinfusion at the end of treatment according to a high risk medulloblastoma protocol. After few months the patients relapsed and at this time an anti-angiogenetic/anti-tumor program was proposed after ethical consensus. The antiangiogenic therapy included continuous oral administration of thalidomide to suppress the VEGF and bFGF-induced neovascularization and celecoxib to inhibit the COX-2 dependent endothelial cell activation. The microarray analysis was performed as previously described (Eisen et al. Methods Enzymol, 1999; 303:179–205). The analysis was performed using microchips that include 1000 cDNAs. Images were analyzed with GenPix Pro 4.1 software (Axon Instruments, Foster City, CA), and fluorescence ratios was calculated. Moreover, the tumor neoangiogenesis was also characterized by determination of microvessel density and COX2 immunoistochemistry.
Several overexpressed genes were identified and considered for possible targets of specific anti-angiogenetic therapy. All patients showed good levels of expression in all the factors involved in the neo-vascularization