1229 ORAL

Adult neuroblastoma patients have inferior survival to pediatric patients and infants: SEER data

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Purpose: Clinical data on survival outcomes of adult patients (defined as aged 20 years and older) with neuroblastoma are scarce due to the rarity of the disease. Small single institution reports have described worse outcomes for adults than pediatric patients.
Materials and methods: Data from the public-access Surveillance Epidemiology and End Results database were reviewed for the thirty-year period between 1973 and 2002 for the diagnosis of neuroblastoma. Using follow-up data through 2002, survival was examined within four different age groups: infants (12 months or less [n = 700]), young children (1–10 years [n = 1120]), older children (11–19 years [n = 90]), and adults (20 years and older [n = 125]). All results were expressed as three- and five-year observed survival.
Results: The observed three- and five-year survival rates were lowest among adult patients (45.9% and 36.3%). Patients between 1 and 9 years of age and patients 10–19 years of age had intermediate rates with corresponding three- and five-year observed survival rates of 52.9% and 47.8% for younger children, and 61.3% and 46.2% for older children and adolescents. Infants fared best, with 86.0% three-year and 84.6% five-year overall survival.
Conclusions: Adults with neuroblastoma have significantly worse outcome than children. This may be due to tumor biology, more virulent clinical course, or possibly by the fact that adults are less sensitive or have poor tolerance to pediatric chemotherapy regimens.
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Poster presentations (Mon, 31 Oct)
Paediatric oncology

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Chemotherapy strategy for choroid or optic nerve involvment retinoblastoma

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Objective: The aim of the study was the evaluation of chemotherapy regimens based on carboplatin and possibilities for avoiding conventional radiotherapy in patients with bilateral retinoblastoma.
Material and methods: From 1998 to 2004 we treated 22 patients with high risk retinoblastoma (RB), median age 24 months (range 2 months to 7 years), 13 male and 9 female. All patients had tumor invasion into the optic nerve or choroid – 14 unilateral RB (group I), and 8 bilateral RB (group II). There was no leptomeningeal or bone dissemination.
Enucleation of one eye was performed in all patients. Local radiotherapy, range 40 Gy, was applied in all patients in group I and in two patients in group II. In group II, 3 pts had focal treatments (cryotherapy, thermotherapy) combined with chemotherapy. Chemotherapy regimen – Vincristine 1.5 mg/m^2/day 1, Etoposide 150 mg/m^2 days 1 and 2, Carboplatin 560 mg/m^2/day 1 was administered to group I and JET regimen Carboplatin 1000 mg/m^2/day 1 and Etoposide 300 mg /m^2/day 1 in group II.
Results: During the 10 to 71 months follow-up period (Me = 32 months) overall survival (OS) rate was 79.7%. OS was 85.7% in unilateral and 67.9% in bilateral group. Toxic side effects were acceptable, slightly higher in the bilateral group.
Conclusion: Application of chemotherapy regimens based on carboplatin in patients with high risk retinoblastoma is effective. Increased carboplatin dose with or without local ophtalmic treatment could enable avoiding conventional radiotherapy on the other eye in patients with bilateral retinoblastoma.

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TP73 expression in medulloblastoma

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TP73 gives rise to two diametrically opposed protein classes: transactivation–competent p73 proteins (TAp73) and transactivation-deficient NH2-terminaly truncated p73 proteins (ΔTAp73 i.e. ΔNp73, p73ex2, p73ex2/3). TAp73 possesses a putative tumor suppressor activity similar to p53, whereas ΔTAp73 forms act as dominant negative inhibitors of p53 and full-length p73 proteins. Oncogenic activity of ΔTAp73 has been shown and frequent tumor specific up-regulation of ΔTAp73 forms was observed in some cancer, including breast and hepatocellular carcinoma. ΔNp73 overexpression was found to be an independent prognostic marker for aggressive clinical behaviour in patients with neuroblastoma. ΔNp73 is also involved in neural morphogenesis; it is an essential survival protein in central as well in peripheral neurons.
In this study, we hypothesized that p73 might also be involved in medulloblastoma carcinogenesis. Tumor tissue samples from consecutive (n = 18) patients treated according to consistent protocols were obtained at neurosurgery and stored in liquid nitrogen until processing. The diagnosis of medulloblastoma was confirmed by central pathologic review. Isoform-specific (TAp73, ÄNp73, p73ex2/3) real-time reverse transcription-PCR quantification of transcripts was performed. We also examined the expression at the protein level by means of immunohistochemical staging with anti-p73 antibody at corresponding paraffin-embedded samples. Normal human cerebellum tissue was used as a negative control.
Based on observed up-regulation of TP73 transcripts in some tumors, we suggest the involvement of TP73 in medulloblastoma carcinogenesis. Correlations regarding TP73 and relevant clinical data will be presented, however to draw a conclusion about the TAp73 vs. ΔTAp73 interplay pattern and its prognostic significance in medulloblastoma, more samples are need to be analyzed.

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P53 expression does not predict chemotherapy response in paediatric patients with osteosarcoma

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Background: High grade Osteosarcoma (OS) is the most frequent primary bone tumor in patients under 20 years. It is highly malignant tumor and without treatment a lethal disease. Current treatment for OS comprises orthopedical radical surgery and systemic intensive chemotherapy. Prognosis for osteosarcoma depends on clinical facts (site, size and metastasis) and the most conclusive tool to predict prognosis for patients with localized limb disease is the response to neoadjuvant chemotherapy of the primary tumor. P53 gene is a tumor suppressor gene that participates in cell cycle regulation and apoptosis. Its mutations have been related to resistance to chemotherapy and radiotherapy. P53 missense mutations can be indirectly assessed by immunohistochemical expression of p53 protein. We design a study to determine whether p53 expression predicts an inadequate chemotherapy response and poor prognosis for paediatric patients with OS.
Patients and methods: 36 consecutive patients under 20 years with high grade OS were studied. All were treated according to consecutive treatment protocols designed by the Sociedad Española de Oncología Pediatrica (SEOP). Neoadjuvant chemotherapy based on cisplatin, ifosfamide, high dose methotrexate and anthracycline was administered in all cases. p53 expression was assessed in samples from diagnosis and the tumor response was estimated after a 14 weeks neoadjuvant chemotherapy at the primary tumor resection.
Results: The mean age was 11 years old. Event free survival (EFS) was 61.9%±8.8% with median follow up of 27 months and Overall Survival (S) was 60.8%±8.5% median follow up 48 month. 4 patients had metastasis at diagnosis. 21 of 34 patients had good response to chemotherapy (tumor necrosis >90%). 19% of the patients were p53 positive at diagnosis. P53 expression was not related with poor response to chemotherapy and did not have any influence on prognosis. The most significant prognostic factors were metastasis at diagnosis (HR 8.41, p = 0.02) and chemotherapy response (HR 5.61, p = 0.02).

Conclusions: The immunohistochemical expression of p53 protein does not seem to predict tumor response to chemotherapy and does not have any influence in prognosis for children with OS. The most reliable prognostic factors were the presence of metastasis at diagnosis and the tumor necrosis after chemotherapy. There is a need to search for earlier prognostic factor in children with OS.

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Temozolomide in resistent or relapsed neuroblastoma

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Purpose: We report the results of a feasibility study of a study investigating the role of oral temozolomide (TMZ) in relapsed or resistant neuroblastoma at the dosage of 215 mg/m^2/day × 5 days, or 180 mg/m^2/day × 5 days in pts with prior autologous bone marrow transplantation (ABMT).
Patients and methods: 17 children with resistant or relapsed neuroblastoma were enrolled. 12 had bone marrow involvement and 5 had localized disease. All pts were pre-treated, 106 outpatient courses were administered, with a median of 4.8 courses/pt.
Results: Overall response-rate (CR+PR+MR) in our series was 11.7% (1 CR, 1 MR), SD was observed in 9 patients and PD in 6. The median survival was 7.8 months (range 1–41). Bone marrow responses were 1 VGPR, 1 PR, 5 SD and 5 PD, according to INRC. We have 1 CR and 1 AWD at 37 and 41 months respectively. Haematological toxicity grade 3–4 was observed.
Conclusion: The results obtained in patients with NB, suggest that TMZ might be useful in the setting of minimal residual marrow disease control. Combination therapy with other agents should also be investigated.

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5 years results of complex treatment high-risk medulloblastoma in children older 3 years with protocol M-2000

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Materials and method: 93 patients with high-risk medulloblastoma 3–15 years of age (median 8 years), 64 boys and 29 girls, were randomized: 46 patients received cyclic polychemotherapy (PCT), 47 – supporting. 19 patients had total removal of the tumor, 74 patients – subtotal. Mts (stages M1-M3) at the time of the diagnosis were found in 52 patients (M1 – 2 patients, M2 – 8 patients, M3 – 22 patients). Radiotherapy (RT) were started at 14–21 days after surgery: craniospinal 35 Gy, posterior fossa – 55 Gy, bust on Mts 10 Gy; with VCR 1.5 mg/m^2 weekly and CCNU 100 mg/m^2 on week 1 of RT. PCT carried out on 4 weeks after RT. Cyclic PCT – 2 alternating cycles each 3 weeks, altogether 4 cycles (1-st cycle: VCR 1.5 mg/m^2 days 1, 8 and Cph 1500 mg/m^2 days 1, 2; 2-nd cycle: VP-16 150 mg/m^2 days 1, 2, 3 and CDDP 70 mg/m^2 day 1). Supporting PCT – 8 cycles each 6 weeks (VCR 1.5 mg/m^2 days 1, 8, 15, CCNU 75 mg/m^2 and CDDP 70 mg/m^2 day 1).
Results: Overall response was seen in 87 patients: CR – 82 (94.3%) patients; PR – 3 (3.4%) patients, 2 (2.3%) patients had PD. Median observation – 19 months. PFS and OS at 5 years – 78±0.07% and 887plusmn;0.04%, respectively. PFS was higher in patients without Mts – 91% vs. with Mts – 53% ($d < 0.05$). PFS was higher in children older 6 years, than under 6 years: 81% and 75%, respectively ($d < 0.05$). Patients who have received the protocol without reduction of RT or/and PCT dozes and in timing according to the protocol had the best PFS: 91% vs. 57% ($d < 0.01$). There was no statistic difference in PFS between patients who received cyclic or supporting PCT (73% vs. 85%, $d < 0.9$). The volume of surgical removal (total or subtotal) had no influence on PFS (60% vs. 83%, $d<0.05$).

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Catheter-related thrombosis in children with solid tumor

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Aim: to determine the prevalence of catheter-related thrombosis in children with cancer.
Patients and methods: children with solid tumor and central venous lines (CVLs), admitted as day care in a period of 3 months, were consecutively enrolled. All the patients (pts) were evaluated by physical examination and biochemical serum analyses including fibrinogen and antithrombin tests. Vessels patency and wall regularity were evaluated by grey scale and eco-color-doppler ultrasonography. Thrombophilia factors were studied in pts with venous thrombosis (VT), both symptomatic and asymptomatic. Thirty-three pts (10 females and 23 males) – mean age 115 months (range 6–252) were enrolled. They were affected by Neuroblastoma (10), Sarcoma (7), Brain tumor (5), Lymphoma (6), Epatoblastoma (1), Langherans' cells histiocytosis (1), Retinoblastoma (1), Malignant Teratoma (1), Wilms' tumor (1). The mean duration of catheter placement was 7 months (range 1–19). Thirty-one pts had Groshong CV 5 Fr or 7 Fr and 2 Broviac 4.2 Fr. No pt received L-asparaginase; 11 pts received corticosteroid therapy.
Results: Four of 33 (12%) pts had VT, 3 of these had asymptomatic and catheter-related VT visualized by sonography, while 1 pt had clinically symptomatic and no catheter-related VT. All these pts received thrombophilia tests that showed: – Abnormal prothrombin gene (prothrombin G20210 A) in 1 pt – Mutation of Plasminogen activator inhibitor-1 (PAI-1): mutation of 4G/5G with hypofibrinolysis in one pt-Hyperhomocysteinemia correlated with MTHFR mutation with T677 and A1298C variants in one pt – Factor V Leiden presence (G1691A) and factor V mutation H1299R) in one pt.
Conclusion: 1) In our series, 12% of pts presented VT. 2) VT was asymptomatic and catheter-related in 10%. 3) In all of these pts thrombophilia genetic risks were found.
CVLs is related to an increasing risk of thrombosis in children with solid tumors. The clinical relevance of genetic risk has to be estabilished. Prospective and multicentric studies are required in order to select patients need prevention strategies.

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FDG-PET imaging for staging and follow-up of malignant paediatric sarcomas: preliminary results of a prospective multicenter study

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Aim: PET evaluation for staging and therapy control of pediatric sarcomas.
Material and methods: In this study 16 patients (9f, 7m; mean: 12.8y., range 1–17y.) with sarcoma (Osteosarcoma n = 4, Ewing n = 7, Rhabdomyosarcoma n = 5) were enrolled. A total of 41 PET scans for staging (n = 16), therapy monitoring (n = 16) and restaging at least 3 weeks after therapy (n = 9) were performed. Results were compared with conventional imagine modalities (CIM: ultrasound, chest X-ray, CT, MRI) according to EURO Ewing 99, COSS 96 and CWS 02P. Histology (n = 12) and/or clinical and imaging follow-up (n = 15) served as reference endpoint.
Results: For detection of primary tumours PET and CIM were equally effective as all 16 histologically proven primaries were found by either method. 8/16 pts. had initially detected metastases (lung n = 2, regional n = 2, distant and/or multiple n = 6). PET revealed 8 pts. true pos. suffering of metastatic diseases but did not discover two lung metastases. CIM however, detected these lung metastases true pos. and 3 other pts. with multiple lesions, although not as extensively as PET.
PET diagnosed 14 pts. with complete (n = 6) and partial (n = 8) therapy response while primary tumour showed significant ($p<0.001$) reduction of SUV_{max} (initial SUV: 8.2 vs. restaging SUV: 2.7). CIM did not correctly diagnose tumour response during therapy in 4 pts. By final examination PET assumed residual lesions in two pts. which must be considered false pos. presently. By CIM residual disease was suspected in 4/9 pts. So far, clinical follow-up did not show any recurrency in all 9 pts., although a larger observation time (presently mean 218 days) is needed.
In summary, PET caused a change of therapy in 7/16 children. 6 received a more intensive therapy due to initial PET and one pt. underwent a less intensive therapy due to metabolic response in PET.