SOLID NON BRAIN TUMOURS

NEUROBLASTOMA

ABSTRACT NO.: O-082

Segmental chromosomal alterations have prognostic impact in primary and relapsed neuroblastoma patients

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Key words: copy number variations, prognosis, primary neuroblastoma, relapsed neuroblastoma

Introduction. Neuroblastoma is characterised by wide clinical heterogeneity caused by the genetic features of the tumor. Segmental chromosomal abnormalities or copy number variations (CNVs) are common alterations in the neuroblastoma genome. At the same time the prognostic significance of many CNVs remains unclear.

Aim. Investigation of spectrum, frequency and prognostic impact of CNVs in primary and recurrent neuroblastomas.

Materials and methods. 139 primary and 22 relapsed neuroblastoma samples were studied for CNVs using MLPA. All primary and 14 relapsed tumors were obtained during core biopsy. In 8 cases of recurrence liquid biopsy of involved bone marrow has been performed. Prognostic significance was estimated by overall (OS) and event-free survival (EFS) with median of follow-up time 36 months (range 1–190 months).

Results. In 32 patients (23.0 %) 1p deletion was revealed and had negative prognostic impact (EFS 0.38 SE 0.09 vs. 0.63 SE 0.05, $P = 0.010$, OS 0.49 SE 0.09 vs. 0.71 SE 0.05, $P = 0.008$). 17q gain was detected in 60 patients (43.2 %), EFS 0.51 SE 0.07 vs. 0.63 SE 0.06, $P = 0.041$, OS 0.51 SE 0.08 vs. 0.74 SE 0.06, $P = 0.021$. Trisomy 7 discovered in 12 patients (8.6 %) decreased survival: EFS 0.41 SE 0.16 vs. 0.59 SE 0.05, $P = 0.032$; OS 0.46 SE 0.18 vs. 0.65 SE 0.05, $P = 0.045$. Aberrations listed above retained prognostic significance in MYCN non-amplified patients.

2p23-24 gain below the MYCN amplification (MNA) level was detected in 13 patients and had negative significance in group of patients below 18 moths: both EFS and OS 0.56 SE 0.20 vs. 0.82 SE 0.06, $P = 0.048$ and 0.92 SE 0.04, $P = 0.024$.

9p deletion with haploinsufficiency of CDKN2A gene was revealed in 9 patients (6.5 %) and resulted in low OS 0.38 SE 0.17 vs. 0.65 SE 0.05, $P = 0.032$. MDM2 gene gain had negative influence on EFS in favorable groups: in infants (0.55 SE 0.13 vs. 0.86 SE 0.06, $P = 0.011$), in patients with localized disease (0.61 SE 0.11 vs. 0.79 SE 0.06, $P = 0.057$) and in 4S patients (0.20 SE 0.18 vs. 0.86 SE 0.13, $P = 0.043$).

In multivariate analysis of OS stage 4 ($P = 0.042$), MNA ($P = 0.049$) and 9p deletion ($P = 0.041$) demonstrated independent prognostic significance.

Investigation of CNVs in relapsed neuroblastomas revealed appearance of new alterations in 9, stable spectrum of aberrations in 3 and lack of original CNVs in 5 cases. Patients harboring new CNVs had significantly worse outcome after the recurrence comparing with those who had identical or lack of CNVs in relapse: EFS 0.00, OS 0.14 SE 0.13 vs. both 0.73 SE 0.16, $P = 0.014$, $P = 0.045$.

Conclusion. Thus CNVs have prognostic significance in primary and relapsed neuroblastomas. This fact encourages performing tissue or liquid biopsies in cases of the tumor recurrence.

ABSTRACT NO.: OP-089

Stromal Collagen type XI alpha 1 COL11A1 expression in neuroblastoma

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Key words: neuroblastoma, high-risk, MYCN, chromatin remodeling

Introduction. In invasive carcinomas, the extracellular collagens are key players of tumor behavior and are subjected to continuous remodeling in tumor progression, recurrence and poor outcome. The COL11A1 human gene codes for the α1 chain of procollagen and mature-collagen 11A1, an extracellular component of ECM. It has been reported that high expression COL11A1 participates in many cancers and is correlated with clinico-pathological features, suggesting its value as a useful prognostic factor for cancer patients. However, such study is not yet investigated in Neuroblastoma, the most aggressive and heterogenous cancer in children.
Aim. The aim of this study is to clarify the COL11A1 expression and its relation with Neuroblastoma outcome in Vietnamese patients.
Materials and methods. A total of 80 NB patients in Children Hospital II were enrolled in this study. The expression levels of COL11A1 genes were measured using quantitative reverse transcription polymerase chain reaction (qRT-PCR). Immunohistochemistry was used to localize COL11A1 expression in tumor or stroma region. Association with clinoco-pathological NB and COL11A1 were assessed in specimens collected from primary, metastases and recurrent NB.
Results. COL11A1 expression was detected in 23 % of 83 NB and correlated with stage 3/4 ($P = 0.23$), recurrence ($n = 8$, $P = 0.01$), MYCN amplification ($P = 0.04$). Immunostaining showed that the COL11A1 co-localized with Vimentin in intratumoral stroma, but not the peripheral stroma. Remarkably, such COL11A1 mRNA expression is significantly associated with MYCN amplification.
Conclusion. Our findings examine the COL11A1 expression in advantaged cancer and suggest that microenvironment of stromal COL11A1 is a significant risk for cancer prognosis and disease progression.

ABSTRACT NO.: PP-095

Treatment of patients with neuroblastoma stage 4S

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Key words: neuroblastoma, 4S stage, risk group, survival

Introduction. In this study, we examine the prognostic risk factors in patients with neuroblastoma stage 4S, evaluate the results of treatment in this group.
Aim. To improve the survival of patients with stage 4S neuroblastoma.
Materials and methods. The study included 9 patients with neuroblastoma stage 4S, the average age of 5.6 (2–9) months. According to the classification of Y. Shimada in 7 patients had a favorable histology, 1 patient – unfavorable and in 1 case study was not performed. DNA Index: 8 cases was the ploidy hyper detected in tumor cells, and only in 1 case – hypoploidy. The most common sites of metastasis are liver ($n = 8$), and bone marrow ($n = 7$), 89 and 78 % respectively. 6 patients entered the intermediate-risk group, 3 patients – at low risk. 7 patients received radical surgery. 1 patient at low risk and 6 patients in the intermediate-risk group received chemotherapy. No patient received radiation therapy.
Results. 7 patients had obtained a complete remission, 2 patients received a good partial response. Currently, all patients were alive with no evidence of recurrence. Overall survival was 100 % with an average follow-up of 93.4 ± 18,7 months.
Conclusion. In the group of patients with neuroblastoma stage 4s can achieve excellent treatment results. Moreover, radiation therapy (which can lead to disability or development of second tumors) is not necessary. For the same reason, you should avoid intensive chemotherapy, however, such an approach is possible with the correct stratification of risk group and consideration of all prognostic factors.

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ABSTRACT NO.: PP-109

Curative effect analysis of sequential autologous stem cell transplantation on high-risk neuroblastoma in children

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Key words: sequential autologous stem cell transplantation, high-risk, neuroblastoma

Introduction. Nowadays, the prognosis of high-risk neurobalstoma is poor, although with comprehensive treatment of operation, chemotharepy, radiotharepy. We analyse the outcomes of combining sequential autologous stem cell transplantation and traditional therapy.

Aim. To assess the outcomes of sequential autologous stem cell transplantation on high-risk neuroblastoma in children.

Materials and methods. There are 82 high-risk neuroblastoma between January 2010 and December 2014 in our hospital. Of which, 45 patients had accepted stratification treatment according to CCCG-NB09 Protocol, and 16 patients finished sequential autologous stem cell transplantation after chemotherapy and operation. There was 3 months interval between two times ,we gave them radiotherapy. When two times transplantation finished, they accepted orally retinoic acid 6 months.12 patients finished two times sequential autologous stem cell transplantation.

Results. The Kaplan–Meier curve revealed regular therapy according to CCCG-NB09 Protocol significantly improve the prognosis of high-risk neuroblastoma. The median overall survival time of 45 children who received regular therapy was 23.0 months, average survival was 25.1 months, the 1–4 year survival rate was 86.7 %, 70.6 %, 50.6 %, 40.6 %, the response rate (CR+PR+SD) reaches upto 95.5 %.The side effects mainly were reversible bone marrow suppression and digestive tract reaction, not death relating to transplantation and second cancer. We found 3-year total survival (59.7 %) after sequential autologous stem cell transplantation was superior to no transplantation (48.6 %). But the Log-rank test showed there was no significant significance ($P = 0.185$).

Conclusion. Sequential autologous stem cell transplantation on high-risk neuroblastoma in children was superior to no transplantation, but the difference was not significant. So, we need to improve conditioning regimen.

ABSTRACT NO.: OP-122

Expression of CD133, CD24 in neuroblastoma and prognostic significance

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Key words: CD133, CD24, neuroblastoma, prognosis

Introduction. Neuroblastoma (NB), which originates from the sympathoadrenal lineage of neural crest during the embryonic period, is one of the most common extracranial malignant solid tumors in children. The characteristic features of NB are high degree malignancy, early multiple metastases, easy resistance to chemotherapy, and high rate of recurrence. Stem cells is a kind of primitive cells that are: (1) self-renewing, (2) multipotent, and (3) differentiating. Recently, more and more evidence, suggests that very few cancer stem cells exist in the tumor tissue, has been emerging. These cancer stem cells provide a reservoir of cells that can self-renew, maintain the tumor by generating differentiated non-stem cells which make up the bulk of the tumor and are responsible for recurrence after surgery and chemoradiotherapy. A new theoretical basis has been provided for the in-depth study of tumorigenesis and the evaluation of prognosis of cancer therapy. Also, new ideas which target killing cancer stem cells have been introduced for cancer therapy. The aim of our study was to investigate the expression of CD133, CD24 in NB and also analyze the clinical and prognostic significance, looking for new treatment targets of recurrent and refractory NB.

Aim. To investigate the expression of CD133, CD24 in NB and its correlation with clinicopathological factors and prognosis.

Materials and methods. The expression of CD133, CD24 in 78 specimens of NB were assessed by immunohistochemistry.

Results. CD133 was expressed in 55.1 % (43/78) cases of NB, significant association of its expression in NB tumor tissues with INSS Staging ($P = 0.037$), tumor diameter ($P = 0.040$), pathologic types ($P = 0.019$) were found. CD24 was expressed in 60.3 % cases of NB, significant association of its expression in NB tumor tissues with age ($P = 0.008$), INSS Staging ($P = 0.001$), bone metastasis ($P = 0.005$), pathologic types ($P = 0.038$), preoperative chemotherapy ($P = 0.027$) were found. The survival time of CD133 negative patients was significantly longer than that of CD133 positive patients ($P = 0.000$). The survival time of CD24 negative patients was significantly longer than that of CD24 positive patients ($P = 0.001$). Age more than 1 year, recurrence and CD133 expression were independent prognostic factors in NB ($P = 0.037$, 0.001, 0.001, respectively).

Conclusion. Age more than 1 year, recurrence and CD133 expression were independent prognostic factors in NB, NB cells of $CD133^+$ provide new potential targets for killing tumor stem cells.

ABSTRACT NO.: OP-172

Incidence and management of chyle leaks following surgery for abdominal neuroblastoma

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Key words: neuroblastoma, chyle leak, abdominal surgery, conservative treatment

Introduction. Surgical intervention forms an important part of the therapeutic plan for neuroblastoma. However, surgery can be formidable considering the proclivity of these tumors to encase important vascular structures, which makes the resection technically challenging, and often associated with complications. Chyle leak because of disruption of retroperitoneal lymphatic channels is a possibility, however, its incidence and management after surgery for abdominal neuroblastoma is inadequately documented.

Aim. We analyzed our observations to find risk factors and the optimal management of chyle leaks following resection of abdominal neuroblastoma. Second, we also evaluated the impact of chyle leaks on further therapy, local control, and outcome.

Materials and methods. One hundred sixty patients who underwent surgery for abdominal neuroblastoma between September 2004 to August 2014 were evaluated. To find the oncological implication we evaluated the delay in starting further treatment, local control, event free and overall survival.

Results. Chyle leak was the most common complication (20 %). The median measure of leakage was 100 ml/day and it persisted for a median of 12 days. All patients were managed conservatively except one who needed exploration for wound dehiscence. Number of lymph nodes resected was the only factor associated with the risk of chyle leaks ($P = 0.013$). Adjuvant chemotherapy was not delayed in any patient because of chyle leaks per se and the local control, event free and overall survival was not different for patients with and without chyle leak.

Conclusion. Chylous leakage is a common postoperative complication of abdominal neuroblastoma, predisposed by the number of lymph nodes resected. It responds to conservative management and does not compromise the further oncological treatment and outcome hence; it should not be a deterrent to complete surgery.

ABSTRACT NO.: PP-192

Characteristics and results of the treatment of patients with intermediate-risk neuroblastoma in the Republic of Belarus

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Key words: neuroblastoma, intermediate risk group, prognosis

Introduction. Until 2008 in RSRC DOHI the intermediate risk group included patients with neuroblastoma of stage 2B or 3, and patients under 1 year of age with stage 4 disease were treated according to EINS protocol in which a high-dose polychemotherapy (PCT) with the support of autologous hematopoietic stem cell transplantation (auto-HSCT) was used as a consolidating therapy. Since 2008 the intermediate risk group has included: patients with stage 2 or 3 disease with the presence of 1p deletion, patients over 2 years of age with stage 3 disease, patients under 1 year of age with stage 4 disease (MYCN-negative) according to the NB-2004m protocol criteria. They receive treatment designed for the intermediate risk group under the NB-2004m protocol, without auto-HSCT.

Aim. To estimate how changes in the stratification of risk groups and therapy have influenced the outcomes of the treatment of intermediate risk group.

Materials and methods. One hundred forty protocol and observed patients who received treatment according to the NB-2004m protocol at the State Institution "RSRC DOHI" from 2008 until 2016. A study group includes 22 patients of intermediate risk group. Fourteen (63.7 %) of them are boys and eight (36.3 %) are girls. Age distribution – from 4 days to 7 years and 2 months, median age – 9.2 months.

Results. Patients from intermediate risk group amounted to 15.7 % ($n = 22$) of all the patients with neuroblastoma, patients from low risk group – 45.7 % ($n = 65$), patients from high risk group – 40 % ($n = 56$). Distribution of patients according to stages was the following: stage 2 – 2 (9 %), stage 3 – 11 (50 %), stage 4 (children under 1 year of age) – 9 (41 %). Cytogenetic features: 1p deletion – 2 (9 %) patients, triploid tumours – 9 (41 %), di-tetraploid tumours – 13 (59 %). The best resection was the following: total resection – 6 (27.3 %), subtotal resection – 12 (54.5 %), tumour biopsy – 4 (18.2 %). An overall survival (OS) depending on a risk group was: 98 ± 2 % in the low risk group, 77 ± 9 % in the intermediate risk group, 44 ± 10 % ($P = 0.0001$) in the high risk group. Event-free survival (EFS): 92 ± 4 % in the low risk group, 72 ± 10% in the intermediate risk group, 37 ± 8 % ($P = 0.0001$) in the high risk group. Cumulative recurrence rate was: 4.2 ± 2.9 % in the low risk group, 14.8 ± 8.1 % in the intermediate risk group, 59.1 ± 8.4 % ($P = 0.001$) in the high risk group. Toxicity-related death was: 3.6 ± 2.6 % in the low risk group, 13.6 ± 7.5 % in the intermediate risk group, 2.2 ± 2.2 % ($P = 0.065$) in the high risk group. High risk of mortality associated with treatment toxicity was registered in the intermediate risk group due to the death of 2 patients with stage 4 disease (children under 1 year of age) caused by infectious toxicity and the death of 2 patients being under tumour induction. The comparison of the outcomes of the treatment according to the previously used protocols for intermediate risk groups (stage 2B and stage 3 irrespective of patients' age) including patients under 1 year of age with 4 stage disease and the outcomes of the intermediate risk group treatment according to NB-2004m protocol has shown the following: OS in patients treated under the NB-2004m protocol – 77 ± 9 % vs previously used protocols – 78 ± 6 % ($P = 0.7910$); EFS in patients treated under the NB-2004m protocol – 72 ± 10 % vs previously used protocols – 74 ± 6 % ($P = 0.8391$). The outcomes of the treatment of children under 1 year of age with stage 4 according to EINS protocol used until 2008 and the outcomes of the therapeutic strategy used in NB-2004 group are the following: OS in patients treated under the NB-2004m protocol – 68 ± 16 % vs EINS – 50 ± 20 % ($P = 0.7742$); EFS in patients treated under the NB-2004m protocol – 53 ± 17 % vs EINS – 50 ± 20 % ($P = 0.9840$).

Conclusion. The changes of intermediate risk group criteria through including a prognostically more unfavourable category of patients did not result in worse treatment outcomes of the intermediate risk group. Patients under 1 year of age with stage 4 disease who receive treatment in this group do not require auto-HSCT but optimization of accompanying therapy.

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ABSTRACT NO.: OP-226

Outcomes of children with intermediate risk neuroblastoma: Experience from a tertiary cancer centre in India

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Key words: neuroblastoma survival, intermediate risk neuroblastoma, complete resection, gross total resection

Introduction. Patients with intermediate risk (IR) neuroblastoma generally have a favorable outcome; however, the intensity of treatment to achieve this outcome has been debatable. In regards to the extent of surgical resection, conflicting results exist for both complete and incomplete resection.
Aim. To analyze the survival outcomes for patients with IR neuroblastoma and to study the impact of complete resection on the survival.
Materials and methods. Prospectively maintained database of patients who underwent surgery for neuroblastoma between January 2005 and January 2015 at a tertiary centre was analyzed. Patients with Imaging Defined Risk Factors (IDRF) underwent biopsy prior to induction chemotherapy, while those with no IDRF were subjected to primary surgery. he Kaplan–Meier method was used to compute the survival curves, while the log-rank test was used to analyze it.
Results. Of 229 patients with neuroblastoma who underwent treatment, including surgery, 75 patients had IR tumors. After a median follow up of 46 months, the 5-year overall survival and event-free survival was 88.6 %, and 77.6 % respectively. There was no difference in survival between patients who underwent complete resection as compared to those who underwent lesser degrees of resection ($P = 0.789$). There was no significant difference in the incidence of intraoperative complications between patients who underwent complete resection as compared to near complete resection ($P = 0.638$).
Conclusion. The extent of resection does not influence the survival of IR neuroblastoma, especially when multimodality therapy is the norm.

ABSTRACT NO.: PP-241

Neuroblastoma with asymptomatic epidural extension: prolonged survival with palliative care

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Key words: neuroblastoma, epidural involvement, long term follow up, natural history

Introduction. Neuroblastoma is often progressive with poor prognosis despite intensive treatment. However, neuroblastoma in infant may regress spontaneously. Epidural extension of abdominal neuroblastoma often cause spinal cord compression and may need surgical intervention. There is few long-term information on asymptomatic intraspinal neuroblastoma.
Aim. We report here a case of abdominal neuroblastoma with extension into spinal canal but no cord compression symptom who elected for observation only and showed no progression over 6 years.
Materials and methods. A 12-month old child presented with abdominal mass protuding through the right side of his back. He had a severe coarctation of aorta (COAT) with ventricular septal defect and patent ductus arteriosus (PDA) which were diagnosed and had COAT repaired with division of PDA during early infancy. A biopsy of back mass reveal neuroblastoma. He was given 14 courses of a chemotherapy regimen which included vincristine, doxorubicin, cyclophosphamide, & carboplatin every 3 weeks over a-12 month period. A follow-up CT scan and an MRI of the abdomen at age 2 showed minimal response with large residual abdominal mass infiltrating right iliopsoas and paraveterbral muscles, circumferentially encasing aorta and inferior vena cava, with intraspinal extension through widened neural formamina of T12-L5. An MRI of the spine showed. There was lateral displacement the thecal sac without spinal cord compression. At age 2, the child could walk for a few steps but no weakness nor incontinence. The child was referred to our hospital for surgical intervention but the mass was determined to be unresectable and parents refused further chemotherapy as it impaired his quality of life and opted for palliative care. He was followed up bi-annually by clinical examination only. Molecular details of neuroblastoma biopsied specimen will be available at the time of presentation.
Results. The child developed normally over the follow-up period of 6 years. Parents reported great quality of life without medical interventions. There was clinical signs of spinal compression during the observation period. A complete MRI of the abdomen and spine at age 7 1/2 year revealed only slightly enlarged abdominal mass infiltrating the right paravertebral muscle with the same degree of intraspinal extension through widened neural foramina of T12-L5, without spinal cord compression.
Conclusion. Asymptomatic epidural extension of neuroblastoma may not need intervention. A watchful waiting approach is feasible.

ABSTRACT NO.: OP-251

Treatment of high-risk neuroblastoma: experience of Russian federal centers

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Key words: neuroblastoma, high-risk, high-dose chemotherapy

Introduction. The prognosis of patients with high-risk neuroblastoma remains poor. The results of treatment of this group of patients in Russia are not fully studied.

Aim. The aim of the study was to analyze the results of therapy of high-risk neuroblastoma in three federal centers in Russia.

Materials and methods. 270 patients with NB were treated for the period 01.2012–06.2015 (42 months). The diagnosis has been established on the basis of the international criteria (G. Brodeur, 1993). Patients were stratified and treated according to the German NB-2004 protocol. 94 (34.8 %) patients were stratified for the high-risk group. High-dose preparative regimens included carboplatin/etoposide/melphalan (CEM) (till June 2013) and treosulfan/melphalan (TreoMel) (since July 2013). Since July 2014 patients with clear MIBG-positive residual primary tumor and/or metastases prior to hematopoietic stem cell transplantation (HSCT) received ^{131}I-MIBG-therapy.

Results. Male: female ratio was – 1.18:1. The median age at the diagnosis was 32.0 months (range 1.3–128.4). MYCN amplification was observed in 43 (45.7 %) cases. 82 (87.2 %) patients had stage 4 NB. Induction therapy was completed in 90 (95.7 %) patients. 4 patients (all stage 4) didn't complete the induction therapy (2 – progression, 2 – surgical complications). Median number of chemotherapy cycles prior to transplantation was 6 (range 6–10). 78/90 (86.7 %) received high-dose chemotherapy: 28 – CEM, 50 – TreoMel. Contraindications for HSCT included tumor progression ($n = 7$), organ toxicity ($n = 3$), surgical complications ($n = 2$). Transplant-related mortality was 3/78 (3.8 %), all in CEM group. 3-year EFS was 34.4 ± 6.3 % and 3-year OS – 46.6 ± 7.5 %. Stage significantly predicted EFS (stage 1–3, 4S – 81.4 % versus stage 4 – 25.8 %, $P = 0.007$) in the high-risk NB patients. In patients with stage 4 NB ($n = 82$) MYCN amplification was observed in 31/82 (37.8 %), osteomedullary metastases in 73/82 (89.0 %) patients. Induction therapy was completed in 78 (95.1 %). 9 (11.0 %) patients progressed during the induction. Complete, very good partial response and partial response were achieved in 68 (82.9 %) patients. 66/82 (80.5 %) patients received HSCT. 14/82 (17.0 %) with MIBG uptake after the induction received ^{131}I-MIBG-therapy. Analyses of prognostic factors in stage 4 NB showed that non-osteomedullary metastases ($P = 0.01$), MYCN amplification ($P = 0.03$) and progression on the induction ($P = 0.00006$) were associated with inferior EFS in univariate analysis. In the multivariate analysis, pattern of metastases and response to the induction were the most significant variables associated with EFS. 3-year EFS and OS in the cohort of stage 4 patients was25.4 ± 6.8 % and 37.9 ± 8.5 %. Median time to relapse was 14.2 months (range 0.8–32.3 months). Most relapses were systemic (22, 55.0 %) or combined (16, 40.0 %).

Conclusion. Our results are consistent with other research groups. Intensive therapy allows achieving satisfactory results of therapy in high-risk NB patients with stages 1–3 and 4S. The introduction of novel therapies are urgently required to improve prognosis in stage 4 NB.

ABSTRACT NO.: P-254

Epidural compression at the onset of neuroblastoma

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Key words: epidural compression, neuroblastoma, children

Introduction. Neuroblastoma (NB) is the most common extracranial solid tumor of childhood. Neurological symptoms as a result of epidural compression (EC) by tumor are frequent initial presentation of NB.

Aim. To analyse the frequency, clinical presentation and therapeutic tactics in patients with NB and EC.

Materials and methods. The study included 18 children with NB during the period 01.2012–09.2015 (45 months). Diagnosis of EC has been established on the conclusion of the neurological examination and neuroimaging data. All patient were assessed according to the standardized protocol and the diagnosis was established based on histological examination and laboratory findings.

Results. EC in the onset of the disease occurs in 18 of 277 (6.4 %) children with NB. The male: female ratio was 1:1.5. Median age was 8.5 month (range 0.5–85.3 months).

The most common topography of the primary tumor was retroperitoneal space in 12/18 (66.7 %) , posterior mediastinum in 6/18 (33.3 %) cases. EC was often found in patient with stage 3 (6/18 – 33.3 %) and stage 4 (6/18 – 33.3 %) of disease. Stage 2 was observed in 4/18 (22.2 %) and stage 4S stage in 2/18 (11.2 %). Risk group distribution: low risk group – 1/18 (61.1 %), 5/18 (27.7 %) – intermediate risk group and 2/18 (11.2 %) – high risk group.

When was collected history of disease, has been established that 4/18 (22.2 %) patients before admission were not examined by a neurologist; unknown date of onset of the disease. In these children EC was diagnosed at the initial examination by a neurologist in the case of after diagnosis of NB. For 14/18 (77.8 %) children time to onset of clinical symptoms till to diagnosis EC was 2.6 months (range 0,4–5,1 months.).

In the study of neurological status in onset of the disease motor and sensitive dysfunction was found in 18/18 (100 %) cases. In 4/18 (23.5 %) children disease motor and sensitive dysfunction combined with bladder and bowel dysfunction. For 8/18 (44.4 %) patients found disturbances in motor/sensitive sphere and radicular syndrome. Among motor disorders in 3/18 patients (16.7 %) –monoparesis lower limb; y 1/18 (5.5 %) – tetraparesis; y 14/18 (77.8 %) – paraparesis lower limb.

Surgical treatment to resection the tumor from the spinal canal, performed 7/18 (40 %) patients (4 of them received additional chemotherapy). Chemotherapy according to risk-group 10/18 (55.5 %) patients. Surgery to resection only the tumor of the posterior mediastinum performed in 1/18 (5.5 %) patient.

For this time alive 16/18 (88.9 %) patients. Died of complications related to the treatment 2/18 (11.1 %) patients. The duration of follow-up was 24 months (range – 0.1–35.7 months).

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Neurological status after a specific therapy is presented in the form of improvement of motor functions in 5/16 (31.2 %) patients; in 11/16 (68.7 %) noted the preservation of paresis to 4 score and bladder and bowel dysfunction.

Conclusion. In children with EC, to assess the degree of severity of the neurological manifestations needed work out and introduction into clinical practice a standardized scale, perform of additional methods of examination, including in a multi-disciplinary group with neurosurgeon and rehabilitologist. Patient management tactics is determined taking the duration and severity of symptoms EC, stage of disease and risk groups, the presence of the clinic experience of conducting such patients, the possibility of neurosurgical operations.

ABSTRACT NO.: PP-256

Retrospective comparison of treosulphan/melphalan versus carboplatin/etoposide/melphalan as preparative regimen for autologous transplantation in pediatric neuroblastoma

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Key words: high-risk neuroblastoma, autologous stem cell transplantation, preparative regimen

Introduction. High-dose chemotherapy with autologous stem cell transplantation is a standard component of multimodality treatment for high-risk neuroblastoma. Common high-dose preparative regimens for neuroblastoma include busulphan/melphalan (Bu/Mel), carboplatin/etoposide/melphalan (CEM) and TBI-based combinations. Definitive comparison of alternative preparative regimens has not been performed thus far.

Aim. In the current study we analyse retrospectively the results of autotransplantation with two regimens, CEM and treosulfan/melphalan (Treo/Mel), used consecutively for conditioning in patients with high-risk neuroblastoma.

Materials and methods. Fifty six patients with high-risk neuroblastoma were treated in the Federal Center for pediatric hematology and Russian children's hospital since April 2012 till September 2015. All patients were treated according to the NB-2004 protocol, excluding MIBG therapy, which was not available till July 2014. Nine patients were treated according to the NB-2004 protocol, including MIBG therapy, since July 2014 till September 2015. But these patients are not included in this study. Two types of preparative regimens were used. Twenty eight (f-7, m-21, median age 2.53 years) recieved CEM regimen (since September 2012 till June 2013): Melphalan 45 mg/m^2/day, day -8,-7,-6,-5, Etoposide 40 mg/kg, day -4, Carboplatin 500 mg/m^2/day, day -4,-3,-2, G-CSF 10 mcg/kg/day IV since day +5 till WBC $> 5 \times 10^9$/l. Twenty eight patients (f-14, m-14, median age 2.73 years) recieved Treo/Mel regimen (since July 2013 till September 2015): Treosulfan 14 g/m^2/day, day -5,-4,-3, Melphalan 140 mg/m^2, day -1, G-CSF 10 mkg/kg/day since day +5 till WBC $> 5 \times 10^9$/l. The median dose of infused CD34$^+$ cells was 10 (3.5–26) $\times 10^6$/kg and 7.55 (2.7–31) $\times 10^6$/kg respectively. The groups were balanced for disease stage, response to induction therapy and bone marrow involvement. There was a trend towards overrepresentation of MYC-N amplification (68 % vs. 46 %, $P = 0{,}073$) in the CEM group.

Results. Primary engraftment was achieved in 53 of 56 pts, the median time to neutrophil and platelet recovery was 10 and 15 days in the CEM group, 11 and 13.5 days in the Treo/Me group, respectively. In the CEM group 3 pts died of bacterial sepsis before 100-day after SCT, 1y. pTRM – 10.6 % (95 % CI: 3.7–31.2). None of the patients died of transplant complications in the Treo/Mel group, 1y. pTRM 0 %. In CEM group (median follow-up 3,2y) at 2 year cumulative incidence of relapse is 53.6 % (95 % CI: 38–73.8), pEFS is 35.7 % (95 % CI: 18–53.5), pOS – 67.9 % (95 % CI: 50.6–85.2). In the Treo/Mel group (median follow-up 1.77y) 2 year cumulative incidence of relapse is 50.5 % (95 % CI: 34–75.1), pEFS is 51.3 % (95 % CI: 30.9–71.7), pOS – 87.4 % (95 % CI: 73.9–100). There is a trend towards improved overall survival ($P = 0{,}043$) in the Treo/Mel group.

Conclusion. In this retrospective analysis Treo/Mel preparative regimen was associated with improved short-term results in comparison to the more conventional CEM regimen in high-risk neuroblastoma. Further observation, matched pair analysis and prospective testing will be performed to confirm these results and account for potential bias.

ABSTRACT NO.: OP-303

Minimal invasive surgical treatment of children with thoracoabdominal localization

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Key words: neuroblastoma, minimal invasive surgery, children, oncology, laparoscopy, thoracoscopy

Introduction. Minimal invasive surgical treatment is becoming more common in pediatric oncology. One of the perspective directions is a videoendosurgical treatment of children with thoracoabdominally localized neuroblastoma (NB).

Aim. Surgical treatment improvement in children with NB of thoracoabdominal localization.

Materials and methods. From January, 2012 to January, 2016 (48 months) 197 patients received a surgical treatment in the extent of NB resection. Endosurgical operation was undertaken in 54 (27.5 %) patients. All patients were observed and received a treatment according to NB-2004 protocol. For all patients a complex examination was undertaken, surgical risks (IDRF) evaluation was carried out, therapeutic approach was accepted on a interdisciplinary discussion. Endosurgical treatment indication was: the absence of surgical risks (IDRF), previous traumatizing surgical interventions, anatomically localized tumor of up to 7 cm in diameter.

Results. Median age was 20 months (range – 1–96 months), under 1 year – 26 (48 %) children. Stage distribution/allocation: 1st – 29 (54 %) patients, 2nd – 11 (20 %), 4th – 10 (18.5 %), 4S stage – 4 (7.5 %). Thoracoscopic tumor resection was performed in 14 (26 %) patients, laparoscopic tumoradrenalectomy – 36 (66.6 %), laparoscopic resection of paravertebrally localized tumor – 4 (7.4 %). Tumor volume – 1 to 7 cm in diameter. Average surgery duration was 119 minutes. 2 (3.7 %) cases of hemorrhage were reported

intraoperatively, that required a conversion and hemostasis, in 2 (3.7 %) cases the conversion was performed because of complications of tumor isolation. In 1 (1.8 %) female patient an early postoperative period was complicated by sepsis, in 4 (7.4 %) patients Horner's syndrome was reported after thorascopic tumourectomy. In 1 (1.8 %) patient adhesive small bowels obstruction was developed, that required a second-look surgery. Early postoperative period proceeded faster and easier after minimal invasive treatment: early terms of removing from an artificial lung ventilation, less expressed pain syndrome, early activation, cosmetic effect. Follow-up median was 16.2 months, local relapse was reported in 1 (1.8 %), that required a second-look upfront surgery.

Conclusion. The minimal invasive surgery of children with thoracoabdominally localized NB, with contraindications and surgical risks (IDRF) absence, is highly effective method, that allows to perform ales traumatic radical surgery with cosmetic effect and without oncological prognosis decrease.

ABSTRACT NO.: OP-305

Combination of chemotherapy and targeted therapy in treatment of very high-risk patients with neuroblastoma and Ewing sarcoma family of tumors

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Key words: neuroblastoma, Ewing sarcoma, resistant and refractory, chemotherapy, targeted therapy

Introduction. Neuroblastoma (NB) is the most frequently seen pediatric extracranial tumor, while Ewing sarcoma family tumors (ESFT) are second most common bone malignancy. Although the implication of intensive multimodal treatment programs allowed achieving an improvement in overall treatment results, there are still small therapy-resistant subpopulations with dismal prognosis and very short life expectancy.

Aim. Investigating the effectiveness of chemotherapy combination with targeted agents in very high-risk and heavily pretreated patients with NB and ESFT.

Materials and methods. A total of 40 patients with NB ($n = 32$) or ESFT ($n = 8$) received therapy in our department in July 2009 – December 2015. All patients belonged to very high-risk group due to primarily disseminated disease with multiple bone lesions ($n = 29$), primary resistance to 2 or more lines of chemotherapy ($n = 25$) including autologous ($n = 14$) or allogeneic ($n = 6$) hematopoietic stem cell transplantation (HSCT), 1st resistant relapse ($n = 9$), 2nd or further relapse ($n = 9$). Most (35 of 40) patients previously had no response to standard topoisomerase I inhibitors-based therapy. Most patients had progressive disease ($n = 22$), others had PR ($n = 10$) or stabilization ($n = 6$). Two patients received preemptive therapy post-HSCT. Therapy consisted of sirolimus (1 mg/m^2 × 4), dasatinib (2 mg/kg × 4) with consequent irinotecan (50 mg/m^2 × 5) and temozolomide (150 mg/m^2 × 5). The median number of courses given was 3 (range 1–12). All patients with measurable lesions ($n = 39$) were restaged based on RECIST 1.1 criteria after each 2 therapy courses. For NB patients with I-MIBG avid lesion ($n = 23$) ^{123}I-MIBG scintigraphy was also used. Some patients with good response proceeded to high-dose consolidation with autologous ($n = 7$) or allo-HSCT ($n = 4$).

Results. Therapy was effective in 32 of 40 patients (CR in 12.5 %, PR in 32.5 %, and stabilization in 32.5 % of cases), although the effect was mostly short lasting with a median of 3 (2–48) months. Only 7 (17.5 %) of 40 patients are currently alive with a median follow-up of 10 (4–52) months. While in NB patients CR or good PR was observed in 19 of 32 (60 %) cases only 5 of 8 ESFT patients achieved a short-term stabilization. As expected, patients with progressive disease had worse (40 %) response rate, although in 2 cases CR was observed. All patients with less aggressive disease responded for a median of 8 (2–48) months in spite of previous ineffective exposure to topoisomerase I inhibitors. High-dose consolidation in good responders ($n = 11$) was ineffective, all but one patient relapsed in a median of 8 (4–39) months. One of post allo-HSCT preemptive therapy recipients died of acute graft-versus-host disease, another is alive and stable 42 months after HSCT. The therapy regimen toxicity was relatively mild, even in HSCT recipients with hematological toxicity critical for therapy timing developing in 4 and severe irinotecan-associated diarrhea in 6 cases.

Conclusion. Combination of irinotecan-based chemotherapy with sirolimus and dasatinib allows achieving response in very high-risk patients with NB in spite of previous resistance to topoisomerase I inhibitors, although in resistant ESFT cases its advantage over standard therapy is not evident. However, results achieved are mostly short-termed in spite of dose-intensive consolidation. The regimen toxicity is relatively mild; its low hematological toxicity allows employment in post-HSCT settings.

ABSTRACT NO.: PP-333

Vascular "Image-defined risk factors" in abdominal neuroblastoma that were determined by ultrasound

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Key words: neuroblastoma, ultrasound, image-defined risk factors

Introduction. The most common sites of origin of neuroblastic tumors are the adrenal region and extraadrenal retroperitoneum (65–73 %). Clinical stage is currently the most statistically significant and clinically relevant prognostic factor. In parallel, can be used IDRFs – image-defined risk factors by Consensus Report from the International Neuroblastoma Risk Group Project (2011). Stage L2 tumors by IDRFs are local-regional tumors with one or more IDRFs. While metastatic disease (stage M or MS) is staged oblivious of the local-regional tumor extent, the absence or availability of an IDRFs for the primary tumor must always be assessed to aid surgical decisions.

Aim. The purpose of the study was to determine the frequency of vascular IDRFs in patients with abdominal neuroblastoma through capability ultrasound.

Materials and methods. Were studied result of ultrasound examination of 32 children aged from 0.1 to 10 years (mean 3.0 ± 2.5) with a prospectively established diagnosis of

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neuroblastoma of the adrenal region and extraadrenal retroperitoneum in stage 1–4, 4s (ISSN). Ultrasound data were verified by comparing with the results of computer tomography.
Results. Mean tumor volume in patients amounted 350 ± 314 cm^3. Abdominal aorta and it branches were involved in the tumors of the extraadrenal retroperitoneum in 82 % cases and in the tumors of adrenal region – in 30 % cases. The anterior displacement of abdominal aorta from 3–4 mm till centimeters (mean 12 ± 8 mm) in 50 % patients with the spread of the tumor under aorta was confirmed. Tumor encasing origin of celiac axis and/or origin of superior mesenteric artery was in of 46 % all cases, tumor invading one or both renal pedicles was in 38 % cases, tumor encasing aorta and/or vena cava was in 53 %. Simultaneous involvement of all of the above vessels was in 23 %. In one case we observed the invasion of a tumor in the inferior vena cava. It has been found that the angle of divergence of the superior mesenteric artery and the aorta in patients with tumor of extraadrenal retroperitoneum bigger than in the patients with tumors of adrenal region ($P = 0.02$). On the data of the Power Doppler and pulsed-wave Doppler were noted intratumorally branching vessels, irregular diameter of the vessels, arteriovenous shunts in the tumor. In the cases with the calcification of neuroblastoma the vascularization of tumor was a low. In the remaining cases were determined by the average degree of tumor vascularization. The mean values of resistance index for vessels within the tumor was 0.64 ± 0.15.
Conclusion. The ultrasound duplex scan is the useful method in determining the involvement of major vessels of abdominal aorta in the retroperitoneal tumor. The ability to accurately quantify to define the indicators such as the anterior displacement of abdominal aorta and the angle of divergence of the superior mesenteric artery and the aorta in patients with tumor of extra adrenal retroperitoneal increases the value of the method. The constitutional features of the childhood allow easy to select of the optimal acoustic windows for ultrasound investigation to obtain precise contours of the vascular tree, which is particularly useful for the dynamic assessment of the tumor during chemotherapy.

ABSTRACT NO.: PP-371

Introduction the ^{131}I-MIBG therapy in treatment of patients with high risk group neuroblastoma in Russian Federation

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Key words: neuroblastoma, ^{131}I-MIBG, childhood cancer
Introduction. The long term survival in high risk group patient's with neuroblastoma (NB) is very poor, which become a reason to intense the therapy. The ^{131}metaiodobenzylguanidine (^{131}I-MIBG) therapy is one of the options to improve treatment results in this patient's group, after induction therapy.
Aim. To analyze indications for ^{131}I-MIBG therapy application in group patient's with NB within multicenter interaction.
Materials and methods. 14 patients with high risk group NB were included into our research. Observation period was from 07.2014 to 12.2015 (18 month). All the patients received therapy according to NB-2004 protocol. The ^{131}I-MIBG positive lesions (primary tumor/metastasis) which had been detected after induction therapy became the indication for using ^{131}I-MIBG therapy. Quantitative evaluation lesions of pathological accumulation radiopharmaceuticals, was used during the metaiodobenzylguanidine (MIBG) scintigraphy (Curie score). The dose of radiopharmaceuticals was 12 mCi/kg during the ^{131}I-MIBG therapy.
Results. The average age was 39.8 month at the primary diagnostic (from 18.4 to 64.4). Seven patients (50 %) had retroperitoneal primary tumor localization, 6 (42.9 %) – adrenal glands, and in one (7.1 %) case in posterior mediastinum area. All the patients were diagnosed 4 stage of the main disease. Twelve patients (85.7 %) had the bone marrow metastasis, 11 (78.5 %) – in bones, 7 (50 %) – in lymph nodes, 1 (7.1 %) – in liver and 1 (7.1 %) in lungs. Bone marrow and/or bones were affected with metastasis in thirteen patients (92.8 %). The MYCN amplification was observed in 4 (28.5 %) cases.
Twelve patients (85.7 %) recived ^{131}I-MIBG therapy after 6 courses of induction therapy, 2 (14.3 %) – after 8 courses. The median days from the last course of chemotherapy to ^{131}I-MIBG therapy was 30 days (from 22 to 42 days). MIBG positive lesions from primary tumor and metastasis were observed in 5 patients (35.7 %), 4 (28.6 %) had MIBG positive residual tumor (without any accumulation in metastatic areas), and 5 patients (35.7 %) had MIBG positive only metastatic lesions (without accumulation in primary tumor area). The dose of radiopharmaceuticals in all cases was strict - 12 mCi/kg. After ^{131}I-MIBG therapy any complications were not observed. All the patients received autological stem cell transplantation after ^{131}I-MIBG therapy. The median from day of ^{131}I-MIBG therapy to conditioning was 13 days (from 10 to 21 days). The median of engraftment was 11 days (from 9 to 16 days). Veno-occlusive disease was not observed in any case. The average follow up period was 11.9 month (from 7.7 to 19.3). Twelve patients (85.8 %) have being survived without any events, 1 patient (7.1 %) – have being survived after the progression of the disease, 1 (7.1 %) died after the progression of the main disease.
Conclusion. Our investigation demonstrated the ability to introduce the new treatment method for patients with high risk neuroblastoma, within multicenter and multidiscipline cooperation in Russian Federation. The designed algorithm of prospective planning and patient's selection for ^{131}I-MIBG therapy allows to include the new method to the multimodal therapy without infringement of timing. The long follow up period allows to evaluate the influence of therapy option into the main disease prognosis.