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PROGRAM AND ABSTRACT BOOK

Methods and population:
94 MYCN-A infants (58 males, 36 females) were considered eligible, (75% stage 4; 13% stage 2-3, 12% 4s) with a median age of 8.5 months. All received induction chemotherapy (IC: Rapid-Cojec ± TVD) followed by BuMel/SCT, primary site surgery, radiation (21Gy) and 13-cisRA as maintenance. 35 received antiGD2 ch14.18/CHO treatment since 2010. Median follow up time is 3.9 years. In 99.4 trial, 35 patients (20 males, 15 females; median age 7,6 months) were analyzed (69% stage 4, 28% stage 4s and 3% stage 3). Treatment consisted in standard IC (carboplatin&etoposide-CADO), surgery, BuMel/SCT, local radiotherapy, 13-cisRA maintenance (JCO 2009).

Results: For HR-NBL1, 85% of evaluable cases (n=80) achieved CR/VGPR/PR following IC. Six infants went off treatment, one had PD whilst five had less than PR. The EFS and OS rates are 0.44±0.06 and 0.48±0.06 for all 94 MYCN-A infants. The 5 yr EFS and OS rates were 0.4 and 0.45 for stage 4; 0.51 and 0.51 for stage 2&3, 0.58 and 0.65 for stage 4s (NS). The main cause of death remained progression/relapse, while only 4 cases were due to toxicity. For 99.4 population, 30% of patients progressed/did not respond to IC, with median time to progression of 4 months. The 2y-OS was 28% (SD: 0.15), 2y-EFS 24% (SD:0,11) , 12 months median survival time.

Conclusions: Rapid-Cojec resulted in less disease progressions and better response rate than 99.4 IC. Although OS and EFS improved in HR-NBL1/ SIOPEN as compared to 99.4, it is below 50% with lack of disease control being the main cause of death. The number of infants treated with ch14.18/CHO is too small to conclude currently and will be further addressed.

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Myeloablative busulfan/melphalan (BuMel) consolidation following induction chemotherapy for patients with high-risk neuroblastoma. A Children's Oncology Group (COG) study.

Meaghan Granger[1], Arlene Naranjo, Jeanine S McCune, Steven G Dubois, Ro Bagatell, Brian D Weiss, Steven A Grupp, Sheena C Cretella, Yael P Mosse, Shahab Asgharzadeh, Michael Hogarty, Joseph Panoff, John Han-Chih Chang, Wendy London, Julie M Gastier-Foster, Denise Mills, Julie R Park, Greg Yanik[2]
Cook Children's Medical Center, Fort Worth, TX, US
University of Michigan, Ann Arbor, MI, US

Background: The COG conducted a groupwide study of a Busulfan/Melphalan (BuMel) myeloablative regimen in patients with newly diagnosed, high-risk neuroblastoma (ANBL12P1). Previously used in SIOP-EN studies, this is the first trial using BuMel following a COG induction platform. The primary objective was regimen-related toxicity, with a specific focus on pulmonary and hepatic events.
Methods: Five cycles of induction were administered, followed by intravenous busulfan (daily, days -6 to -3), melphalan (140mg/m2, day -1) and stem cell rescue. Age and weight based dosing were used for busulfan administration. First dose busulfan pharmacokinetics were mandated and adjustments made to target an AUC
Results: Between 4/2013 and 4/2015, 150 patients were enrolled. One hundred thirteen patients were evaluable for end-induction response assessment, with 27 (25%) CR, 27 (24%) VGPR and 39 (35%) PR, for an overall response rate of 82%. At the time of consolidation, 101 patients are evaluable for toxicity. The incidence of unacceptable pulmonary toxicity was 3.0% (n = 3), SOS 5.9% (n = 6), and combined hepato-pulmonary toxicity 8.9% (N = 9) during consolidation (days 0–28). There were 0 toxic deaths during consolidation. For all subjects (n=98), the median busulfan AUC was 3554 (range: 2360-4555) micromole/liter*minute, with a median AUC of 4558 (range: 3462-5189) micromole/liter*minute for those developing SOS (n =6) and 3232 (range: 3010-5037) micromole/liter*minute for those developing severe pulmonary toxicity (n= 3).
Conclusion: BuMel following COG induction regimen is well tolerated with acceptable pulmonary and hepatic toxicity in high-risk neuroblastoma.

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DFMO maintains remission and increases overall survival in high risk neuroblastoma: results of a phase II prevention trial

Giselle Sholler[1], William Ferguson[2], Genevieve Bergandahl[1], Jeffrey Bond[3], Kathleen Neville[4], Don Eslin[5], William Roberts[6], Randal Wada[7], Javier Oesterheld[8], Deanna Mitchell[1], Jessica Foley[1], Valerie Brown[9], Nehal Parikh[10], Francis Eshun[11], Peter Zage[12], Jawhar Rawwas[13], Susan Sencer[13], Debra Pankiewicz[14], Monique Quinn[14], Maria Rich[1], Joseph Junewick[15], Max Wicha[16], Jacqueline Kraveka[17]
Helen Devos Childrens Hospital, Grand Rapids, MI, United States
Cardinal Glennon Children's Hospital, St. Louis, MO
University of Vermont, Burlington, VT
University of Arkansas, LIttle Rock, AK
Arnold Palmer Hospital for Children, Orlando, FL
Rady Children's Hospital San Diego, San Diego, CA
University of Hawaii, Honalulu, HI
Levine Children's Hospital, Charlotte, NC
Penn State Milton S. Hershey Medical Center and Children's Hospital, Hershey, PA
Harford Children's Hospital, Hartford, CT
Phoenix Children's Hospital, Phoenix, AZ
Texas Children's Hospital, Houston, TX
Children's Hospitals and Clinics of Minnesota, Minneapolis, MN
Michigan State University College of Human Medicine, Grand Rapids, MI
Advanced Radiology Services, Grand Rapids, MI
University of Michigan, Ann Arbor, MI
Medical University of South Carolina , Charlston, SC

Background: High Risk Neuroblastoma (HRNB) remains a challenge in pediatric oncology, accounting for 15% of all pediatric cancer deaths. While most patients are able to attain remission, the natural history of HRNB is well documented with approximately half of patients relapsing within 5 years after completion of immunotherapy. This study evaluated the effectiveness of the ODC inhibitor

difluoromethylornithine (DFMO), which targets cancer stem cell pathways in HRNB, as a maintenance therapy to prevent relapse in HRNB patients who were in complete remission at the completion of standard therapy.
Methods: This study was an open label, single agent, multicenter study. Enrollment began in June 2012 and ended in February 2016. Subjects received 27 4-week cycles of oral DFMO at a dose of 500-1000 mg/m^2 twice daily. Event free survival (EFS) and overall survival (OS) were determined on an intention-to-treat (ITT) basis.
Results: A total of 94 subjects received DFMO, 91 were eligible for the intention to treat (ITT) population. For all ITT subjects, EFS was 91% (± 4%) and OS 98% (+/-2%) at 2 years. For the subgroup of subjects (n=74) who were previously enrolled on the ANBL0032 study, the 2 year EFS was 95% (± 3%) and OS 98% (+/-2%). This is a significant improvement in comparison to ANBL0032 study which showed a conservative EFS of 76% 2 years post antibody therapy (p <0.01) and OS of 89% (p
Conclusions: Administration of DFMO at 500-1000mg/m^2 BID is an effective and safe dose. Following the completion of standard therapy for high risk neuroblastoma DFMO treatment was associated with improved EFS and OS decreasing the high rate of relapse in children with HRNB. An additional prospective trial is ongoing to confirm these results.

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The benefit of myeloablative chemotherapy with autologous stem cell transplantation in high-risk neuroblastoma patients is stable during long term follow-up. Results of the NB97 trial.

Thorsten Simon[1], Barbara Hero[1], Ruth Volland[1], Angelika Eggert[2], Frank Berthold[1]
University of Cologne, Cologne, NRW, Germany
University Hospital, Charite, Berlin, Germany

Background: Randomized trials have demonstrated improved survival of high-risk neuroblastoma patients after myeloablative chemotherapy (MAT) with autologous stem cell transplantation (ASCT) compared to oral continuation chemotherapy (CC). This effect, however, could either be due to better cure rates or to delay of relapses. Therefore, we have re-analyzed the patient cohort of the randomized trial NB97 in order to find whether the survival benefit of MAT and ASCT is stable during long term follow-up.
Methods: Patients with stage 4 neuroblastoma older than 12 months and all patients with MYCN amplification were eligible. Treatment consisted of six-cycle induction chemotherapy, primary site tumor resection, consolidation either with MAT/ASCT or CC, MIBG therapy for MIBG avid residual disease, radiation therapy for active local disease present after operation, and post-consolidation therapy either with single drug anti-GD2 antibody ch14.18 or with 13-cis-retinoic acid. Outcome was analyzed by logrank test and Cox regression analysis.
Results: A total of 295 patients were randomized. The median observation time was 11.6 years. The 10 year event-free survival (10yEFS) was 40.0+/-4.0% in 149 patients randomized for MAT and 29.4+/-3.8% in 146 patients randomized for CC (p=0.027). The 10 year overall survival was 55.2+/-4.1% and 44.6+/-4.2% in patients randomized for MAT and CC, respectively (p=0.077). The last relapse occurred 12.7 years after diagnosis, so far. In the subgroup of stage 4 patients >18 months at diagnosis randomization for MAT was associated with better EFS (p=0.023) and a trend for better OS (p=0.098). Multivariable analysis identified stage, MYCN status, age, MAT, and treatment with ch14.18 as independent prognostic factors for EFS and also for OS.
Conclusion: Intensive multimodality treatments can achieve survival rates of 50% in high-risk neuroblastoma patients. The benefit of MAT with ASCT is due to improved cure rates and not to delay of relapses.

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Catecholamine metabolites: novel diagnostic insight, correlations with biological features and prediction of clinical outcome in patients with neuroblastoma

Iedan Verly[1, 2], Andre van Kuilenburg[2], Nico Abeling[2], S Goorden[2], Marta Fiocco[3, 4], Fred Vaz[2], Max van Noesel[5], Michel Zwaan[6], Gert-Jan Kaspers[7], Johannes Merks[1], Huib Caron[1], Godlieve Tytgat[5, 1]
Department of Pediatric Oncology, Emma Children's Hospital, Academical Medical Center, Amsterdam, the Netherlands
Laboratory Genetic Metabolic Diseases, Emma Children's Hospital/Academic Medical Center, , Amsterdam, , The Netherlands
Mathematical institute, Leiden University, Leiden, the Netherlands
Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, the Netherlands
Princess Máxima centre for Pediatric Oncology (PMC), Utrecht, the Netherlands
Department of Pediatric Oncology/Hematology, ,Erasmus-MC Sophia Children's Hospital, , Rotterdam, The Netherlands
Department of Pediatric Oncology/Hematology, , VU University Medical Center, , Amsterdam, , The Netherlands

Introduction: neuroblastoma accounts for 10% of pediatric malignancies and is responsible for 15% of pediatric cancer-related deaths. Vanillylmandelic acid (VMA) and homovanillic acid (HVA) are commonly analyzed in urine of neuroblastoma patients, however, their diagnostic sensitivity is quite low and their correlation with clinical outcome is still controversial. Other catecholamines metabolites have hardly been studied and for diagnostic purposes, analysis of a panel of catecholamine metabolites might be more accurate. Therefore, we performed in-depth analysis of the diagnostic sensitivity of catecholamine metabolites at time of diagnosis and their correlation with clinical outcome.
Patients and methods: retrospective study of urinary metabolites (VMA, HVA, 3-methoxytyramine, dopamine, epinephrine, metanephrine, norepinephrine and normetanephrine) from 301 neuroblastoma patients at diagnosis.
Results: normetanephrine was the most sensitive diagnostic metabolite with sensitivity of 89%, improving to 95% when all 8 metabolites were combined. Especially 3-methoxytyramine and