MEDULLOBLASTOMA

MB-01. INVOLVEMENTS OF hsa-miR-383 AND ITS TARGET PEROXIREDOXIN 3 (PRDX3) IN CONTROLS OF MEDULLOBLASTOMA CELL GROWTH
Karl C. Wai,1 Jesse Chang-Sean Pang,1 and Ho-Kueang Ng2; 1Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong; 2State Key Laboratory in Southern China in of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong

Medulloblastoma (MB) is the most common brain cancer. Recent advances in cancer biology strongly suggest that impaired microRNAs expression is one of the critical events driving cancer development. Previous studies of microRNA expression profiling suggested hsa-miR-383 as one of the down-regulated microRNAs in MB. However, the functions of this microRNA in MB remain unclear. In this study, we demonstrated frequent down-regulation of hsa-miR-383 expression in MB by quantitative stem-loop-RT-PCR analysis. Twenty-three out of 29 (79%) MB samples expressed 2-fold of the lower level of hsa-miR-383 compared with normal cerebellar samples and also limited/nondetectable levels were found in 4 MB cell lines (DA0Y, ONS-76, D283, and D458). Exctop expression of hsa-miR-383 by microRNA mimic significantly inhibited MB cell growth along with its 3'UTR PARP cleavage, suggesting induction of apoptosis in the hsa-miR-383-mimic-treated MB cells and tumor suppressive roles of hsa-miR-383. By transcriptome analysis of hsa-miR-383-mimic-treated MB cells and computational prediction of hsa-miR-383 targets, we identified Peroxiredoxin 3 (PRDX3) as one of the targets with significant down-regulation of expression in the mimic-treated MB cells. Down-regulation was verified at both RNA and protein levels. In addition, the mimc significantly decreased the expression of the reporter that was constructed with the 3'UTR of PRDX3 in MB cells. Site-directed mutation of the predicted recognition site abrogated the reduction, and this demonstrated the specificity of hsa-miR-383-mediated repression on PRDX3 expression in MB cells. Furthermore, siRNA knockdown of PRDX3 resulted in cell growth inhibition and induction of PARP cleavage, mimicking the effects of the hsa-miR-383 restoration by microRNA mimic in MB cells. In conclusion, hsa-miR-383 may function as tumor suppressive microRNA in MB and this is mediated through its target PRDX3 to control MB cell growth.

MB-02. QUESTIONABLE ROLE OF CRANIOSPINAL IRRADIATION (CSI) IN NON CEREBELLAR PNET (NC/PNET) WHEN USING A HIGH-DOSE CHEMOTHERAPY (HDCT) STRATEGY
Maura Massimino1, Lorenza Gandola1, Veronica Biasioni1, Filippo Spreafico1, Elisabetta Schiavello1, Geraldina Poggi1, Michela Casanova1, Emilia Pecori1, Marco Vajna De Pava1, Andrea Ferrari1, Kay Ka-Wai Li1, Jesse Chung-Sean Pang1, and Ho-Keung Ng1; 1Department of Medulloblastoma, Children’s Hospital, Children’s Cancer Hospital, Cairo, Egypt

BACKGROUND: Medulloblastoma patients below 3 years had inferior survival rates due to several reasons. AIM: To investigate the treatment end-results of medulloblastomas under 3 years of age and determine the factors that affects its prognosis. PATIENTS AND METHODS: Eighteen children below the age of 3 years were treated at Children’s Cancer Hospital, Egypt during the period from July 2007 and December 2010. Safe maximum resections were attempted in all patients. Gross total resection was performed in 10 children (56%), subtotal excision in 7 children (39%) and biopsy in one patient. Fourteen children (78%) proved to be non-metastatic, while 4 belonged to M3 category (spinal seeding). Eight out of the 18 (44%) children received infantile medulloblastoma chemotherapy protocol, while the other 10 received other chemotherapy protocols. All the 4 metastatic children received craniospinal irradiation (CSI) with boost to the seedling or site of metastasis. Six out of the 10 patients received posterior fossa (PF) irradiation (5580 cGy), while the other 8 received CSI, as they reached the age of 3 years, with booster dose up to 5580 cGy to PF. RESULTS: The 3-year overall survival (OS) for all children was 55 ± 15%. The OS for non-metastatic was 61 ± 15% and 50 ± 29% for M children. The infantile chemotherapy protocol led to 1-year OS of 71 ± 17% compared to 24 ± 18% for other protocols. The OS for CSI was 71 ± 17% compared to 49 ± 23% for conventional PF irradiation. None of the CSI group developed CNS relapse, while only 17% received PF irradiation had spinal relapse. It is worth noting that none of the these detected differences were statistically significant. All children treated with minimal immediate toxicity and acceptable, so far, late effects. CONCLUSIONS: The 3-year OS of children below 3 years were modest with improved OS in non-metastatic patients who received infantile protocol and CSI.

MB-03. MEDULLOBLASTOMA BELOW THE AGE OF 3 YEARS: TREATMENT AND PROGNOSTIC FACTORS
Mohamed Elbeltagy, and Madeha Awaad; Children’s Cancer Hospital Cairo, Egypt

BACKGROUND: Medulloblastoma patients below 3 years had inferior survival rates due to several reasons. AIM: To investigate the treatment end-results of medulloblastomas under 3 years of age and determine the factors that affects its prognosis. PATIENTS AND METHODS: Eighteen children below the age of 3 years were treated at Children’s Cancer Hospital, Egypt during the period from July 2007 and December 2010. Safe maximum resections were attempted in all patients. Gross total resection was performed in 10 children (56%), subtotal excision in 7 children (39%) and biopsy in one patient. Fourteen children (78%) proved to be non-metastatic, while 4 belonged to M3 category (spinal seeding). Eight out of the 18 (44%) children received infantile medulloblastoma chemotherapy protocol, while the other 10 received other chemotherapy protocols. All the 4 metastatic children received craniospinal irradiation (CSI) with boost to the seedling or site of metastasis. Six out of the 10 patients received posterior fossa (PF) irradiation (5580 cGy), while the other 8 received CSI, as they reached the age of 3 years, with booster dose up to 5580 cGy to PF. RESULTS: The 3-year overall survival (OS) for all children was 55 ± 15%. The OS for non-metastatic was 61 ± 15% and 50 ± 29% for M children. The infantile chemotherapy protocol led to 1-year OS of 71 ± 17% compared to 24 ± 18% for other protocols. The OS for CSI was 71 ± 17% compared to 49 ± 23% for conventional PF irradiation. None of the CSI group developed CNS relapse, while only 17% received PF irradiation had spinal relapse. It is worth noting that none of the these detected differences were statistically significant. All children treated with minimal immediate toxicity and acceptable, so far, late effects. CONCLUSIONS: The 3-year OS of children below 3 years were modest with improved OS in non-metastatic patients who received infantile protocol and CSI.

MB-04. MEDULLOBLASTOMA HISTOLOGICAL VARIANTS AS THE MOST POWERFUL CLINICAL PROGNOSTIC INDICATOR: A 10-YEAR MONO-INSTITUTIONAL EXPERIENCE
Maura Massimino1, Lorenza Gandola1, Veronica Biasioni1, Manila Antonelli2, Elisabetta Schiavello1, Francesca Buttarelli1, Filippo Spreafico1, Paola Collini1, Bianca Pollo1, Carlo Patriarca1, and Felice Giangaspero2; Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; 2Neuropalatologia, Universita` La Sapienza, Roma, Italy; 3Anatomia Patologica, Ospedale S. Anna, Como, Italy

BACKGROUND: Histological classification in medulloblastoma has aroused in importance and newer treatment protocols will include histology as risk factor. We centrally revised all our medulloblastoma cases of the last ten years and re-assessed their histology to identify its prognostic importance. METHODS: Patients’ samples were reviewed according to the two subsequent WHO classifications 2000 and 2007. Consecutive patients were 125. RESULTS: Male were 99, non-metastatic were 82, primary tumor was completely resected in 97, 10 patients were under 3-years of age and the different protocols adopted. Histology gave 82% 5-year PFS for all children, 76%, 73% and 81%, respectively. Histology was classic in 93 cases, desmoplastic in 20, anaplastic in 10, medulloblastoma with pineal and hypothalamic extension in 2 each, medulloblastoma with desmoplastic pineal and hypothalamic extension in 1 each, and medulloblastoma with desmoplastic pineal in 1. Seven cases were not classified. Six tumors were metastatic at the time of diagnosis. The 3-year OS was 82% for non-metastatic (M1), 75% for metastatic (M2), and 18% for other protocols (M3). CONCLUSIONS: Histological classification in medulloblastoma is an important factor with potential diagnostic and therapeutic implications. MEDULLOBLASTOMA HISTOLOGICAL VARIANTS AS THE MOST POWERFUL CLINICAL PROGNOSTIC INDICATOR: A 10-YEAR MONO-INSTITUTIONAL EXPERIENCE

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revised anaplasia, that was not considered as such when designing previous trials, remained the most powerful prognostic factor and deserve appropriate treatment intensification.

MB-05. THE APPLICATION OF NANOPARTICLE LIPOSOME-IMPRIME BLUE IN THE TREATMENT OF MEDULLOBLASTOMA IN THE SMAA1 TRANSGENIC MICE

Toby MacDonaldb, Jingbo Liuc, Jenny Munsonc, Jaekeun Parkd, Kewang Wangb, John Fishc, Tao Bakhmadzic, and Jack Arzab2
1Department of Pediatrics, Emory University, Atlanta, GA, USA; 2Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA, USA; 3Department of Biomedical Engineering, Emory University, Atlanta, GA, USA; 4Department of Radiology & Imaging Sciences, Emory University, Atlanta, GA, USA; 5Department of Dermatology, Emory University, Atlanta, GA, USA

Medulloblastoma is one of the most common malignant tumors in children. Its lethality is associated with tumor metastasis and the side effects of available treatment severely affect survivor’s quality of life. Impramine blue (IB), a new anti-tumor drug, is encapsulated with liposome to form a liposomal nanoparticle (Liposome-IB), which has the advantage of reaching the tumor site and extending retention effect. In vitro studies demonstrated that Liposome-IB inhibit the growth and migration of several medulloblastoma cells including Daoy (human) and Ps125 (mouse) in a dose-dependent manner. To determine the responsiveness of medulloblastoma to Liposome-IB treatment. The Liposome-IB treated mice survived significantly longer (median survivals of 82 days) than the control mice (median survivals of 25 days) than the control mice (median survivals of 25 days). The tumor volume progression was monitored by MRI at the different time points after treatment. The results showed that the tumor volume increased dramatically in the control group compared with Liposome-IB treatment group. The Liposome-IB treated mice survived significantly longer (median survivals of 82 ± 21.9 days) than the control mice (median survivals of 25 ± 15.5 days; P = 0.024). In conclusion, the nanoparticle Liposome-IB is effective in the treatment of mouse medulloblastoma in vivo. It can significantly delay the tumor progression and prolong the tumor bearing mice’s survival time. The results provide valuable data in supporting the translation from the preclinical animal model trial to the development of clinical trial and protocol to the cancer patients.

MB-06. HOW TO REDUCE CHEMOTHERAPY FOR LOWER-RISK MEDULLOBLASTOMAS - IMPORTANCE OF INTERACTIONS BETWEEN SURGERY AND ADJUVANT THERAPY

Akira Gomia, Takashi Yamaguchia, Toshihiro Mashikoa, and Keiji Ogurob, Ichij Medical University, Tochigi, Japan

PURPOSE: ICE chemotherapy, comprising ifosfamide, cisplatin, and etoposide, is one of the most common regimens for medulloblastoma in Japan. However, hematological and hearing toxicities are frequently encountered. We report herein a single-institute experience of reduced chemotherapy for lower-risk medulloblastomas. METHODS: Thirteen patients with medulloblastomas treated at our institute from 2000 to 2011 were retrospectively reviewed. Adjuvant treatment was selected based on our new clinical classification. Tumors that have been completely resected, with no residual tumor apparent on MRI, in patients >3 years old with no leptomeningeal dissemination (M0) are classified as “lower risk”. Patients with residual tumors >1.5 cm3 or age <3 years old and show no or only focal dissemination (M0-2) are classified as “average risk”. Patients with residual tumors ≥1.5 cm3, liposominal IB treatment in vivo, were categorized as “high risk”. Seven of the patients received two doses of Liposome-IB by tail vein injection with a 5-day interval. The dosage of Liposome-IB is 4.5mg/kg (liposome-IB / body weight). The mice in the control group received the same amount of Liposome-only. The tumor progression was monitored by MRI at the different time points after the Liposome-IB treatment. The results showed that the tumor volume increased dramatically in the control group compared with Liposome-IB treatment group. The Liposome-IB treated mice survived significantly longer (median survivals of 82 ± 21.9 days) than the control mice (median survivals of 25 ± 15.5 days; P = 0.024). In conclusion, the nanoparticle Liposome-IB is effective in the treatment of mouse medulloblastoma in vivo. It can significantly delay the tumor progression and prolong the tumor bearing mice’s survival time. The results provide valuable data in supporting the translation from the preclinical animal model trial to the development of clinical trial and protocol to the cancer patients.

MB-07. GORLIN’S SYNDROME (GS) AND DESMOPLASTIC MEDULLOBLASTOMA (DBM): REPORT OF 3 CASES WITH UNIQUE TUMOR LOCATION, CLINICAL COURSE, AND NOVEL MUTATION

Arthur Mackinnon1, Bonnie Neuhe1, Gerald Grant1, Herbert Fuchs1, Tim Driscoll2, Oren Becher1, Roger McLendon1, Thomas Cummings1, and Srirahdan Gururangan1
1Duke University Medical Center, Durham, NC, USA; 2South Carolina Cancer Center, Charleston, SC, USA

GS is a genetic condition associated with DBM in 5% of cases. DBM in GS usually occurs in infants and has a good prognosis. Radiotherapy (RT) is usually avoided in these children due to the higher risk of secondary cancers following RT exposure. We present three cases of GS with DBM with unique disease features. Patient #1 with frontotemporal, facial dysmorphism, bifid right 3rd rib, and a spontaneous germline PITCH mutation (C > T, exon 18) underwent gross total resection (GTR) of cerebellar DBM at age 2 years but focally relapsed in the right lateral ventricle following radiation therapy (RT). She underwent GTR of cerebellar DBM at age 2.5 years with no evidence of disease (NED). Patient #2 with mild frontal bossing and large hands and a inherited germ line PTCH mutation (C > T, exon 18) underwent gross total resection of a pineal DBM at age 20 months and found to have a DBM. He underwent GTR followed by HDC + ASCR but had disseminated recurrence 6 months following treatment and subsequently died following palliative RT. Patient #3 with focal dysplasia, bifid right 3rd rib, and a spontaneous germline mutation, c.1670 > G, p. Thr557Arg, presented at age 2.5 years with a cerebellar DBM with excessive nodularity. She underwent GTR of tumor and IC followed by HDC + ASCR and no RT. She is now 10 months old. RT was not given and DBM has a good prognosis, disease progression can occur following initial therapy but can still be controlled using HDC + ASCR without RT. The association of GS with DBM in the pineal region or due to exon 12 1670 C > G, p. Thr557Arg mutation have not been previously reported.

MB-08. MYC AMPLIFICATION CAN BE SAFELY ASSESSED BY ARRAY-CGH IN MEDULLOBLASTOMAS

Franck Bourdeaut, Camille Grison, Francois Doz, Gaelle Pierron, Olivier Delattre, and Jerome Couturier, Inserit Curse, Paris, France

As risk factors for poor outcome, MYC and MYCN amplifications are routinely assessed in medulloblastomas. FISH is considered as the technique of reference. Recently, array-CGH has been developed as an alternative technique to evaluate genomic abnormalities in many other tumor types. However, this technique has not been validated in medulloblastomas. MATERIAL AND METHODS: we systematically compared FISH and array-CGH on a retrospective series of medulloblastomas referred to our institution from 2000 to 2011. FISH were performed on frozen section, using MYC and MYCN probes (Vysis, Abbott Molecular, Des Plaines, IL). Array-CGH were done on home-made BAC-arrays until 2009, and then on 4*72K arrays NimbelGen (Madison, WI). Before DNA extraction, the tumor cellularity was evaluated on a matched frozen section; all tumours showed >80% tumour cells. RESULTS: we screened 72 tumours by FISH; MYC and MYCN amplifications were evidenced in 4 and 7 cases, respectively. In all cases showing amplification by FISH, array-CGH unambiguously revealed the abnormality. As expected, no amplification was detected. Interestingly, one tumour showed a focal MYC amplification by FISH, observed in approximately 20% of tumour cells; this subclonal amplification was clearly evidenced on array-CGH. CONCLUSION: our analysis confirms that array-CGH is as safe as FISH for the detection of MYC genes amplification. Even in case of focal amplification, a theoretical event which is very rare in routine practice, array-CGH is sensitive enough to detect the subclonal amplification. Consequently, the higher sensitivity of array-CGH compared to FISH allows the extension of this technique to other highly amplified genes. We strongly recommend performing both FISH and array-CGH in all routine medulloblastomas investigations.