INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY SIOP XXXII CONGRESS

BOSTON, UNITED STATES OCTOBER 21–24, 2010 SIOP ABSTRACTS

SYMPOSIA LECTURES (SL)

SL005

CELL SPECIFIC GENE EXPRESSION AND WHAT WE THINK WE KNOW ABOUT LCH

C. E. Allen

Baylor College of Medicine, Pediatrics, Houston, United States

Purpose: Langerhans Cell Histiocytosis (LCH) is a rare disease characterized by heterogeneous lesions containing CD207+ Langerhans cells and lymphocytes that can arise in almost any tissue and may cause significant morbidity and mortality. After decades of research, the pathogenesis of LCH remains speculative. This study was performed to test the prevailing model of LCH pathogenesis that lesions arise due to malignant transformation of epidermal Langerhans cells (LCs).
Method: LCH CD207+ cells were isolated from LCH lesions, control LCs were isolated from normal skin, and gene expression was compared. Similarly, gene expression in LCH lesion CD3+ cells was compared to gene expression in peripheral blood CD3+ cells from LCH patients with active disease.
Results: Compared to control epidermal CD207+ cells, the LCH CD207+ cells yielded 2900 differentially-expressed probes. Expression of many genes previously associated with LCH, including cell-cycle regulators, pro-inflammatory cytokines and chemokines were not significantly different from control LCs in our study. The study also identified several interesting genes not previously associated with increased expression in LCH including genes involved in regulation of cell cycle (CDC2A, AFF3, SMYD3, HOXB7), apoptosis (BAX, BCL2L1, CFLAR) signal transduction (DUSP4, JAK3, PRKCA, TLR2, TLR4, SOCS3, JAG2), tumor invasion and metastasis/tissue invasion (CEACAM6, MMP1, TGFB1), myeloid cell maturation (CD1d, CD13, CD14, CD33, ITGA2B, ITGAX, ITGAM, CD300LF) and lymphocyte trafficking (SPP1, VNN1, NRP1, CCR1). A large number of the cells with decreased or absent expression in the LCH-CD207 cells are involved in cell-cell adhesion, including TACSTD1.
Compared to the peripheral CD3+ cells from LCH patients, the LCH lesion CD3+ cells yielded only 162 differentially-regulated probes, and the expression profile of the LCH lesion CD3+ cells was consistent with an activated regulatory T cell phenotype, including increased expression of FOXP3 and CTLA4. SPP1 had the highest relative expression in both LCH lesion CD207+ and CD3+ cells.
IL-17 is a proinflammatory cytokine recently associated with LCH pathogenesis. In this study, IL-17 expression was absent from control and LCH CD207+ cells. Very little IL-17 expression was detected in T cells from LCH lesions, but abundant message was detected from tonsil lymphocytes.
Conclusion: We propose a revised model of LCH pathogenesis in which lesions do not arise from epidermal Langerhans cells, but from accumulation of bone-marrow derived immature myeloid dendritic cells that recruit activated lymphocytes. Until the cell of origin can be identified, perhaps ''LCH'' should return to ''Histiocytosis X''.

SL007

SURGICAL APPROACHES TO THE TREATMENT OF LOW-GRADE GLIOMAS

R. M. Scott

United States

Purpose: To describe recent advances in the neurosurgical treatment of low-grade gliomas in children
Method: The author reviewed 5 years of experience with the use of intraoperative MRI, ultrasound, and image-guidance in the surgical treatment of low grade gliomas
Results: These technologies were deemed to be important in the total excision of these tumors in approximately 50% of surgical candidates.
Conclusion: Technological advances in the operating room appear to have led to greater operative safety and improved surgical results

SL009

LOW GRADE GLIOMA IN CHILDREN: MOLECULAR GENETICS AND NOVEL SYSTEMIC THERAPIES

Olaf Witt[1], Huriye Cin[2], Jan Gronych[2], Marc Remke[3], Hendrik Witt[3], Till Milde[4], Pablo Hernaiz-Driever[5], Andrey Korshunov[6], Peter Lichter[2], Stefan Pfister[3]

[1]German Cancer Research Center, CCU Pediatric Oncology, Heidelberg, Germany
[2]German Cancer Research Center, Molecular Genetics, Heidelberg, Germany
[3]German Cancer Research Center and University Hospital, Molecular Genetics and Pediatric Oncology, Heidelberg, Germany
[4]German Cancer Research Center, CCU Pediatric Oncology and Department of Pediatric Oncology, Heidelberg, Germany
[5]Charite University Hospital, Pediatric Oncology, Berlin, Germany
[6]German Cancer Research Center, CCU Neuropathology, Heidelberg, Germany

Purpose: To give an update on the molecular genetics and novel targeted therapies in pediatric low grade glioma
Method: Using primary tumor material, in vitro and in vivo models, the understanding of the molecular origin of low grade gliomas in children has recently made significant progress with the identification of BRAF/MAPK pathway alterations in a high percentage of pilocytic astrocytoma in children
Results: The first specific mutation identified was the KIAA1549-BRAF fusion protein leading to constitutive activation of the MAPK pathway due to loss of the BRAF auto-inhibitory domain. Subsequently, several other fusion proteins involving BRAF and CRAF as well as activating BRAF mutations were identified pointing towards loss of regulation of auto-inhibition as the common molecular theme in the molecular pathogenesis of pilocytic astrocytoma. Using lentiviral gene-transfer, we for the first time were able to generate a mouse model for pilocytic astrocytoma, that is ideally suited for preclinical testing
Conclusion: As several compounds targeting the BRAF/MAPK pathway are clinically available, novel treatment options for pediatric low grade glioma are beginning to emerge

SL15

CLINICAL RESEARCH IN PEDIATRIC RARE CANCERS

Carlos Rodriguez-Galindo

Dana-Farber Cancer Institute, Pediatric Oncology, Boston, United States

Purpose: Advances in the treatment of rare pediatric cancers are hampered by the low number of patients, which limits the design of effective clinical trials, the use of

DOI 10.1002/pbc.22779
Published online 15 September 2010 in Wiley Online Library (wileyonlinelibrary.com.).

involvement (starting 2004). One patient required general anaesthesia.
Multidisciplinary follow-up includes serial imaging and neurocognitive evaluation in all recent cases.
Total dose 54–55 CGE, conventionally-fractionated, was delivered using mixed photon-proton approach (until 2004), or protontherapy only.
Results: Comparative dosimetry (3DCRT/IMRT/protons) in 2 cases, showed benefit of proton-beams for; critical organs (non-abutting chiasma, brain-stem, cochlea); temporal lobes; whole brain exposure.
At median FU 38 mths [3–163], 2 in-field relapses were observed at 49 and 40 mths and were operated showing necrosis. 1 relapse occurred along surgical access-route after 56 mths. In three cases, cystic component increased during or after protontherapy completion. Monitoring of the cysts showed subsequent shrinkage. All children had hypopituitarism with diabetes insipidus prior PT. No PT-related optic-neuropathy was observed. In children irradiated after several surgeries, neuro-psychological evaluation emphasised altered short-term memory, social and emotional functioning, and significant school difficulties. In children treated prospectively with conservative approach, results show reduced morbidity with lower rate of obesity and behavioural disorders when preserving hypothalamus.
Conclusion: Preliminary results of combined approach with conservative surgery for craniopharyngioma with hypothalamic involvement suggests reduced morbidity without jeopardizing tumour control. Long term follow up is required including longitudinal analysis of neurocognition and quality of life. With the potential to decrease risk of late-sequelae and second malignancies, protontherapy is a promising tool, especially for younger children.

O031

DISEASE CONTROL AFTER REDUCED VOLUME CONFORMAL AND INTENSITY-MODULATED RADIATION THERAPY FOR CHILDHOOD CRANIOPHARYNGIOMA

Thomas Merchant[1], Larry Kun[2], Chia-ho Hua[2], Shengjie Wu[3], Xiaoping Xiong[3], Robert Sanford[4], Frederick Boop[4]

[1]St. Jude Childrens Research Hospital, St. Jude Childrens Research Hospital, Memphis, United States
[2]St. Jude Children's Research Hospital, Radiological Sciences, Memphis, United States
[3]St. Jude Children's Research Hospital, Biostatistics, Memphis, United States
[4]Semmes Murphey Neurologic & Spine Institute, Neurosurgery, Memphis, United States

Purpose: To estimate the rate of disease control after conformal radiation therapy using reduced clinical target volume (CTV) margins and determine factors that predict for tumor progression.
Method: Eight-eight children (median age 8.5 yrs, range 3.2–17.6 yrs) received conformal or intensity-modulated radiation therapy at St. Jude Children's Research Hospital between 1998 and 2009. This included those prospectively treated from 1998–2003 using a 10mm CTV, defined as the margin surrounding the solid and cystic tumor targeted to receive the prescription dose of 54Gy. The CTV margin was subsequently reduced after 2003 yielding two groups of patients: those treated with a CTV margin greater than 5 mm (n = 26) and those treated with a CTV margin less than or equal to 5 mm (n = 62). Disease progression was estimated on the basis of additional variables including sex, race, extent of resection, tumor interventions, target volume margins and the frequency of weekly surveillance MR imaging during radiation therapy. The median follow-up was 5 years.
Results: There was no difference comparing progression-free survival based on CTV margin (>5 mm vs. <5 mm) at 5 years, 88.1 + 6.3% vs. 96.2 + 4.4% (P = 0.6386). There was no difference based the planning target volume (PTV) margin (or combined CTV+PTV). The PTV was systematically reduced from 5 to 3mm during the time period of the study. Factors predictive of superior progression-free survival included Caucasian race (P = 0.0175), absent CSF shunting requirement (P = 0.0066) and treatment protocol (P = 0.0032). Patients whose treatment protocol included a higher number of weekly surveillance MR imaging evaluations had a lower rate of tumor progression.
Conclusion: These results suggest that targeted volume reductions for radiation therapy using smaller margins are feasible and safe but require careful monitoring. We are currently investigating the differences in outcome based on host factors, tumor volume and target volume coverage to explain the results.

O032

EFFECT OF FACTORS RELATED TO SURGERY ON LOCAL RECURRENCE IN WILMS' TUMOR

El-Sayed Ashraf Khalil[1], Shimaa Nassif[2]

[1]National Cancer Institute, Cairo University, Surgical Oncology, Cairo, Egypt
[2]National Cancer Institute, Cairo University, Pediatric Hematology Oncology, Cairo, Egypt

Purpose: To assess the influence of surgery related factors on local recurrence rate in children with Wilms tumor treated with NWTS-5 and the impact of postoperative complications on delayed or reduced intensity of treatment.
Method: Children evaluated in this study were retrieved from the records of NCI, Cairo University.
We identified all randomized and followed patients (eligible patients treated according to the NWTS-5, on whom operative and pathology narratives had been submitted to the statistical center. A total of 62 patients who met these criteria were identified. Local recurrence was defined as recurrence in the original tumor bed, in the retroperitoneum, or within the abdominal cavity or pelvis, but did not include children with hematogenous hepatic metastases only. Special attention was given to surgical complications and its impact on local recurrence rate and the intensity of the postsurgical treatment and on possible late effects, which may affect both morbidity and mortality.
Results: Data sets from 62 of registered patients with Wilms tumor who were treated on the NWTS-5 were evaluated. Median follow-up was 3.2 years. Bilateral Wilms tumor was observed in 6.4% of the cases. Intraoperative tumor rupture rates were 19% in primarily operated patients versus 25% in patients with bilateral tumor after preoperative chemotherapy. The absence of lymph node biopsy (in 12/62 of cases) was associated with an increased relative risk of recurrence, which was largest in children with stage II disease. Delayed or reduced intensity of treatment in children with postoperative complication correlated with lower EFS (p-value = 0.002).
Conclusion: Surgical rupture of the tumor must be avoided as tumor spill proved to be a major factor increasing the risk of local recurrence. Lack of definite data on lymph node status in our patients was positively correlated with increased local recurrence rate though not statistically significant.
Keywords: wilms tumor, surgery, childhood

O033

DECISION ANALYSIS TO COMPARE TREATMENT OPTIONS FOR STAGE I INTERMEDIATE-RISK WILMS' TUMOR

Denis Cozzi[1], Amalia Schiavetti[2], Silvia Ceccanti[1], Simone Frediani[1], Ermelinda Mele[1], Vincenzo Crupi[3], Francesco Cozzi[1]

[1]Sapienza University of Rome, Pediatric Surgery Unit, Rome, Italy
[2]Sapienza University of Rome, Pediatric Oncology Unit, Rome, Italy
[3]University of Florence, Critica Care, Firenze, Italy

Purpose: To test our previous hypothesis that nephron-sparing surgery (NSS) can be a reasonable alternative to nephrectomy (NP) in children with unilateral stage I intermediate-risk Wilms' tumor (WT I).
Method: We analysed the outcome of all children with unilateral WT I treated with NSS, thus far reported in the English literature between 1982 and 2009. A state transition model was used to simulate treatment with NSS associated with pre- and/or post-operative vincristine (v) + dactynomycin (d) (option A) and with multiple treatment options which currently exist. Baseline values were obtained from the literature (NWTS-5, SIOP 93–01, UKW 2–3 and present series). Treatment options included NP only (B), NP + v + d (C), v + d + NP + v + d for 18 weeks (D), v +d + NP + v + d for 4 weeks (E), NP + v (F). We used sensitivity analysis to investigate whether NSS should be considered an unacceptable option.
Results: We collected 85 cases with WT I treated with NSS, including 63 from four multicenter studies and 22 from single institution studies. Four patients had a local relapse, successfully treated with re-excision. One patient died from distant metastases without local recurrence. The patients treated with any of the six strategies had essentially the same local recurrence rate (A = 4.7%; B = 3.9%; C = -; B = 3.8%; E = 3.5%; F = 2.9%) and overall survival (A = 98.8%; B = 98.6%; C = 99.1%; D = 97.1%; E = 95%; F = 85%). Local recurrence and overall survival after NSS would have to be much worse than expected to conclude that NSS is an unacceptable option.
Conclusion: In children with unilateral WT I, NSS does not appear to compromise safety and oncological efficacy. The advantage of this option is preservation of most of healthy kidney parenchyma.

O034

ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA (AIEOP) WILMS TUMOUR 2003 PROTOCOL: SURGERY-RELATED ASPECTS