078 THE ROLE OF FDG-PET SCANNING IN THE TREATMENT OF CHILDHOOD AND ADOLESCENT HODGKIN'S LYMPHOMA

D. Kochouz,1 R. Kuge,1 D. Hasencler,1 J. Landman-Parker,1 M. Nekotina,1 E. Bergsträtten,2 J. Karlen,3 G. Mann,4 A. Fernández-Tejedor,1 S. Puzze,5 A. Hraskova9, A. Fossa7, H. Thomassen12, C. Mauz-Koerzholtz1, W. Balwierz13, W.H. Wallace14
1Dept. of Pediatrics, Martin-Luther-Universität, Halle-Wittenberg, Halle, Germany, 2Dept. of Nuclear Medicine, University of Leipzig, Leipzig, Germany, 3Dept. of Pediatrics, University Children’s Hospital, Leipzig, Germany, 4Armand Trousseau, Hospital d’Enfants, Paris, France, 5Dept. of Ped. Hematology and Oncology, Faculty Hospital Motol, Prague, Czech Republic, 6Dept. of Nuclear Medicine, University Hospital, Basel, Switzerland, 7Dept. of Pediatrics, Martin-Luther-Universität, Halle-Wittenberg, Halle, Germany, 8Dept. of Nuclear Medicine, University of Leipzig, Leipzig, Germany, 9Department for Med. Informatics, Statistics of University of Leipzig, Leipzig, Germany, 10Armand Trousseau, Hospital d’Enfants, Paris, France, 11Dept. of Ped. Hematology and Oncology, Faculty Hospital Motol, Prague, Czech Republic, 12Haematologie, University Hospital Brussels, Brussels, Belgium, 13Pediatric Cancer Unit, Astrid Lindgrens Childrens Hospital, Karolinska University Hospital, Stockholm, Sweden, 14Dept. of Pediatrics, St. Anna Childrens Hospital, Vienna, Austria, 15Dept. of Nuclear Medicine, University Children’s Hospital, Bratislava, Slovakia, 16Dept. of Med. Oncol./Radio-therapy, Rikshospitalen, Oslo, Norway, 17Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, 18Dept. Ped. Oncol., Jagiellonian University, Krakow, Poland, 19Cancer Services, Royal Hospital for Sick Children, Edinburgh, United Kingdom

Introduction: The use of intensive chemotherapy regimens has improved prognosis in patients (pts.) with Burkitt Lymphoma (BL). However, in African countries, such intensive regimens can rarely be given and most pts present with advanced disease. A clinical trial is currently in progress under the auspices of the INACT. Preliminary results are presented.

Patients and Methods: Since Aug. 2004, 205 pts (median age 6.5 years, range 2-28) have commenced first-line treatment (Rx). The majority presented with jaw tumours (63%), abdominal/pelvic disease (55%), lymphadenopathy (21%), oesophageal tumours (19%) or combinations thereof. 11% were known to have CNS disease and 11% bone marrow involvement. Rx comprised: 6 cycles of cyclophosphamide: 1.2 G/m², vincristine: 1.4 mg/m² and methotrexate (MTX): 75 mg/m², with thrice weekly intra-thecal (i/t) MTX+cytosine arabinoside (ara-C). 35 pts with refractory/recurrent disease received 4 cycles of ifosfamide: 1.3 G/m² (with mesna), etoposide: 60mg/m² and ara-C: 10mg/m² + i/t MTX + ara-C and 5 with recurrent disease received repeat first-line Rx. Results: 9 pts are not yet evaluable for response, 4 did not return for evaluation. To date, the response rate to initial therapy is 173/ 192 (90%), CR1/2: PR. 31. There were 13 ‘early deaths’, 5 pts did not respond. 20 pts have relapsed; second CR was achieved in 13/35 pts, of whom 17 are currently alive. EFS is 54% at 1 year and 52% at 2 years. OS is estimated to be 68% at 1 year and 62% at 2 years.

Conclusions: This regimen is feasible and the results to date are encouraging. Provision of drugs and infrastructure (training and salaries for data managers) has enabled a collaborative clinical trial to be conducted.

080 DISTRIBUTION OF X-ALK FUSION TRANSCRIPTS IN PEDIATRIC ALCCL – A BFMR-GROUP ANALYSIS

C. Dann-Muller1, I. Oechsler2, W. Klapper3, W. Woesemann4
1Pediatric Hematology and Oncology, Justus-Liebig-University, Giessen, Germany, 2Pathology, Christian-Albrechts-University, Kiel, Germany

Since the late 1970’s children and adolescents with Hodgkin’s lymphoma have been treated in different national protocols using different strategies. While the overall survival rates are in excess of 90%, an increasing number of patients are presenting with second malignancies occurring within the radiotherapy field over twenty years out from their treatment. In an attempt to limit the number of patients exposed to radiotherapy a European protocol has been developed. The study opened in January 2001 and so far 151 pts have been enrolled. The study treatment includes two (OPEA; early stages), four (two cycles of OPEA and two cycles of COPP/COJAC), intermediate stages) or six (two cycles of OPEA and four cycles of COPP/COJAC; advanced stages) cycles of chemotherapy followed by modified involved field radiotherapy for pts with an inadequate response (as judged by cross-sectional imaging and PET scanning) to the first two cycles of chemotherapy. Pts with an adequate response will not receive radiotherapy. Staging includes conventional radiological imaging (CRI; MRT and CT) and FDG-PET. Involvement of a region is determined by CRI irrespective of FDG-PET results. Only in regions with questionable involvement a negative FDG-PET means no involvement, while a positive PET corresponds to involvement. The results of the first 145 patients staged according to this algorithm and assessed centrally in Halle will be presented. An adequate response is achieved in overall FDG-PET negative regions or in cases of a non-informative PET if these regions are in local complete remission determined by CRI. In the first 117 patients the rate of adequate responses are 34% for early stages, 39% for intermediate and 27% for advanced stages determined by central review at the study office in Halle-Leipzig.

© The Author 2008. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. For permissions, please email: journals.permissions@oxfordjournals.org
Background: 90% of anaplastic large cell lymphoma (ALCL) in children and adolescents are characterized by chromosomal translocations involving the anaplastic lymphoma kinase (ALK). The majority of ALK positive ALCL express NPM-ALK. The exact distribution of NPM-ALK and variant ALK-fusion genes is less clear. We report on the detection of ALK-fusion genes by molecular analyses among German children with ALCL.

Material and Methods: Inclusion criteria were the diagnosis of ALCL by national reference pathology including ALK-staining and the availability of frozen tumor material. First, all tumors were analyzed by Reverse Transcriptase (RT)-PCR for the presence of NPM-ALK mRNA. NPM-ALK negative tumors were reexamined by RT-PCRs detecting ATIC-ALK, CLTC-ALK, TFG-ALK and TMP3-ALK mRNAs. In a third step an ALK specific 5'-Rapid Amplification of cDNA ends (RACE)-PCR was applied to tumors characterized by exclusive cytoplasmic expression of ALK and negative RT-PCR results for the most common ALK variants.

Results: Frozen tumor specimens from 64 ALCL patients were analyzed for the presence/absence of NPM-ALK fusion transcripts. NPM-ALK mRNA was detected in 55 of 65 ALK-positive tumors (87%) of which showed typical nuclear and cytoplasmic ALK staining. 7 (11%) of the remaining 8 ALCL had cytoplasmic ALK staining suggestive of a variant ALK-fusion protein. Two where positive for TMP3-ALK and one expressed ATIC-ALK. ALK specific 5’-RACE-PCR and sequence analysis of the 5’-PCR fragment detect a MYH9-ALK fusion gene transcript in one patient which was confirmed by a specific RT-PCR. RT-PCR did not detect ATIC, TFG, ATIC- and MYH9-ALK fusion transcripts in the remaining 3 tumors. However, an ALK-fusion gene was not detected by RT-PCR’s and 5’ RACE.

Conclusion: In our large cohort of molecularly analyzed pediatric and adolescent ALCL, more than 95% express ALK-fusion transcripts/proteins of which more than 85% are NPM-ALK positive leaving 10-15% variant ALK fusion genes.

081 TOXICITY OF INDUCTION CHEMOTHERAPY REPORT OF THE ALCCL99 RANDOMISED TRIAL

G. Wriedel1, A. Marxgüer2, A. Rosolen1, M. Le Deley3, L. Corral1, M. Pillon1, G. Cazzaniga1, A. Biondi1, T. Griffin4, S. Weitzman2, H. Weinstein3, M. Chang4, R. Hutchinson5

1Dept. of BMT Child Hemato/Oncol, Med Univ, Wroclaw, Poland, On Behalf of European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL), 2Dept. of Pediatric Hematology, Univ. of Padova, Padua, Italy, 3Dept. of Pediatric Hematol Oncol, Justus Liebig Univ, Giessen, Germany, 4Dept. of Pediatric, Addenbrookes Hosp, Cambridge, United Kingdom, 5Clin Res, National Hosp Organization Nagoya Med Center, Nagoya, Japan, 6Dept. of Pädiatrie, University of Amsterdam, Amsterdam, Netherlands, 7Dept. of Paediatric Haematol Oncol, Univ Hosp, Leuven, Belgium, 8Dept. of Pediatr, Univ Gothenburg, Göteborg, Sweden, 9Dept of Pediatr Oncol, IRP, Villejuif, France, 10Dept. of Pediatric, Addenbrookes Hosp, Cambridge, United Kingdom

Introduction: ALCCL99 is a randomised trial for paediatric anaplastic large cell lymphoma based on the EBM protocol. Using a factorial design, comparison was made of two doses and schedules of Methotrexate (MTX) and testing the impact of adding vinblastine (VBL) during induction and as maintenance treatment (Tt). We report the acute toxicity (tox) of induction therapy.

Methods: Before 1st course (c) A, pts were randomly allocated to receive MTX 2g/m2 in 4h with late rescue and with intrathecal MTX (ITX) (MTX1) vs MTX 3 g/m2 in 5h with early rescue, without IT (MTX2). Before 1st c, B, Tt of high risk pts was randomized with or without of VBL. Acute tox was assessed using CTC v2.

Results: Between 1999 and 2005, 352 pts from 175 centres were recruited. Tox assessed during induction therapy related toxicities of induction therapy. Stomatitis was significantly more frequent after MTX1 than after MTX2 c (79% vs 64%). Four pts (3.1%) died of induction treatment-related toxicity. Stomatitis and liver tox was more frequent after c B. Haematol tox and infection 41%; gr3-4 SGOT/SGPT elevation 10%; gr3-4 stomatitis 13%. Weight loss was significantly more frequent after MTX1 vs MTX2 (0.2 mg/kg/dose) during COP reduction (generously supplied by Sanofi-Aventis) with an encouraging objective response rate and an acceptable toxicity profile.

Conclusions: The combination of rituximab and ICE chemotherapy was associated with an encouraging objective response rate and an acceptable toxicity profile.

084 PRELIMINARY RESULTS OF A PHASE II STUDY OF CHEMIMMUNOTHERAPY (RITUXIMAB + FAB CHEMOTHERAPY) IN CHILDREN AND ADOLESCENTS WITH INTERMEDIATE RISK B-CELL NHL: A CHILDREN'S ONCOLOGY GROUP REPORT

S. Goldman1, J. Lynch1, V. Davenport2, S. Perkins1, B. Shlimuz1, W. Sanger1, T. Griffin3, T. Hampshire1, M. Banchet1, M.S. Cairo1

1COG, Children’s Oncology Group, New York, United States

Introduction: Children with intermediate risk (St. Jude stage III/IV) B- NHL have an EFS 89% following Fab chemotherapy but have a moderate risk of acute toxicity (mucositis/infection/prolonged hospitalization) (Patte/Cairo et al Blood 2007, Cairo/ Patte et al Blood 2007). We have previously demonstrated that CD20, the receptor to the antibody rituximab, is expressed in 298% of childhood B-NHL (Perkins/Cairo et al Clin Adv Hem 2003) and that rituximab+CHOP vs. CHOP improved EFS and OS in adults with DLBCL (Coiffier et al NEJM 2002).

Methods: Children with newly diagnosed CD20+ DLBCL and BL, St. Jude stage III/IV, without prior therapy or immunodeficiency, were eligible. FAB Bt chemotherapy (Patte/Cairo et al Blood 2007) served as the backbone with the addition of rasburicase (0.2 mg/kg/dose) during COP reduction (generously supplied by Sanofi-Aventis) and rituximab 375 mg/m2/dose (generously supplied by Genentech) day 1 in

Annals of Oncology
Results: 48 children, median age 11 (1-23) yrs, 4/1 M/F, 59% BL, 24% DLBCL, 5% PMBL, 12% NOS,80/10% stage III/IV, were enrolled in subpilot and pilot. Percent in CR at end of COP, COPADM2 and CYM2 were 10%, 31% and 91%, respectively. The addition of rituximab to the FAB B4 backbone was well tolerated. The incidence of grade III/IV mucositis following induction 1 and 2 was 13.9 and 11.4%, respectively, compared to historical FAB/LMB 96 was 43 and 31%, respectively. There was a 2.5% incidence of TLS during COP + rasburicase reduction phase. There were no SAE definitely or probably attributed to rituximab. Probability of 1 yr EFS was 96% (95% CI: 88, 100%) and no deaths to date.

Conclusion: Rituximab can be safely added to the FAB/LMB 96 B4 chemotherapy backbone in children with intermediate risk B-NHL and is associated with an excellent outcome. Future studies will be required to determine if the addition of rituximab to FAB/LMB 96 B4 backbone will facilitate the reduction in cytotoxic chemotherapy without a diminution in long-term EFS.

085 WHERE IS THE PLACE FOR RITUXIMAB IN THE TREATMENT OF B-CELL NON-HODGKIN LYMPHOMA (B-NHL) OF CHILDREN AND ADOLESCENTS?

C. Patte

CD20, a B-cell marker, is expressed in almost all cases of B-NHL in children: in Burkitt lymphoma/leukemia (BL), by far the most frequent, as well as in diffuse large B-cell lymphoma (DLBCL), which frequency increases during adolescence. Outcome of both entries is similar in children. Rituximab is a monoclonal antibody directed against CD20. Its use remarkably increased during the last years in adult with follicular NHL and in DLBCL after randomised studies showed its efficacy with low toxicity. But in adults with BL, there is no published phase III study. The only randomised study is currently performed in France comparing a treatment based on the paediatric LMB protocol with or without rituximab. In children, successful use of rituximab has been reported in post-transplant lymphoproliferative disorders and autoimmune disorders, but in B-NHL, there are only few individual cases.

This leads to an open discussion on the role of rituximab in childhood B-NHL. There is a need to demonstrate its usefulness and to evaluate its toxicity (unusual toxicity have been reported in children). Several attempts to open phase II studies have been done: A European upfront phase II study for relapsed pts was designed, but it only opened in France and had to close due to the small number of relapsing pts. An upfront phase II is running in BFM centres for newly diagnosed pts. A toxicity study of rituximab combined with the LMB scheme was opened in COG.

It would be crucial to open a phase III to answer the following questions: 1) will rituximab allow to decrease chemotherapy, and therefore acute toxicity (not long term toxicity which is already minimal), in good and average risk pts without jeopardizing survival (EFS ≥ 90%)? But it has to be considered that it is a study of equivalence which needs a large number of pts (about 1000 pts by arm), and that an evaluation of costs and toxicity is necessary. 2) could rituximab allow to increase outcome of high risk pts (EFS ≤ 70%)? But these pts are the minority (< 20%) and mostly CNS positive patients, whereas systemic rituximab has a low penetration rate in CNS.

In conclusion: phases II-III are needed to investigate on the role of this targeted therapy in children, but they are difficult to set up. This is why results of the phase III study ongoing in adults with BL are waited for with great interest.