session 8 – pediatric lymphoma

077 RADIATION THERAPY IN PEDIATRIC HODGKIN DISEASE – WHO NEEDS IT?

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High dose radiation therapy as the sole treatment for Hodgkin disease is not utilized in children and adolescents because of unacceptable toxicity (skeletal, cardiopulmonary). Standard therapy for Hodgkin disease in younger patients consists of chemotherapy and low dose involved field radiation therapy. The number and intensity of chemotherapy cycles is determined by stage, and the presence or absence of B symptoms and bulk disease. Utilizing this approach, cure rates are generally > 90%. The long term complications associated with reduced dose radiation therapy are currently not known. In 1995, the Children's Cancer Group opened a trial for all patients with Hodgkin disease in which patients who attained a complete response to initial, risk adapted, chemotherapy were randomized to receive low dose involved field radiation or no further therapy. A debate ensued as to whether EFS or survival was the appropriate end point for the trial. In the end, it was determined that EFS would be the primary endpoint. Patients achieving a partial response to initial chemotherapy received radiation therapy. Group 1 patients (Stage I,II; no B symptoms, no bulk disease; < 4 nodal regions) received 4 courses of COPP/ABV chemotherapy. Patients with Stage IV disease received 6 cycles of chemotherapy which included high dose Ara-C/VP-16, COPP/ABV, and CHOP. All other patients (Group II) received 6 cycles of COPP/ABV therapy. Complete response was defined as no anatomic evidence of disease or, in the case of a residual mediastinal mass, > 70% reduction and a change from gallium positive to gallium negative. The study was terminated early (1999) when a statistically significant difference in EFS was observed between the radiation and no further therapy arms. At the time of termination, there was no difference in overall survival between the two arms. We have recently updated the results of this study. Two hundred fifty patients were randomized to no further therapy and 250 were randomized to receive involved field radiation therapy. Sixteen patients randomized to receive radiation refused treatment; therefore 234 patients actually received radiation and 266 received no further therapy. At a median follow up of 7 years, the overall EFS and S for the entire cohort of patients was 83.3% and 92.9%. By intent to treat, 7 year EFS was 89.7% for radiation patients and 83.2% for no radiation patients (p=.03). In the as treated analysis, 7 year EFS was 91.1% and 82.4% respectively (p=.003). In an as treated analysis, 7 year S was 97.1% for radiation patients and 95.8% for no radiation patients (p=.53). The question as to whether pediatric patients with Hodgkin disease who achieve a complete response to chemotherapy require radiation therapy cannot be readily answered by statistical analysis. It appears that overall survival is not adversely effected by withholding radiation therapy in this cohort of patients. Radiation will prevent relapse in approximately 10% of patients achieving complete response. If radiation therapy is relatively nontoxic, then radiation is probably reasonable therapy. If, however, reduced dose radiation results in significant long term toxicity such as second malignant neoplasms (particularly breast cancer in females) and cardiopulmonary disease, the no radiation therapy approach would appear to be the best choice. Another way to approach this issue is to recognize that there are multiple prognostic subgroups among patients with pediatric Hodgkin disease. It is conceivable that radiation therapy might prevent more relapses in patients with unfavorable prognostic features. Analyses of the impact of radiation in prognostic groups will be presented. Early response to therapy is an important prognostic factor in many pediatric malignancies. Patients showing a rapid anatomic response and/or a rapid PET scan response to chemotherapy may derive less benefit from radiation therapy than those patients with a slower response who eventually achieve a complete response.

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

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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 openedin January 2007 and so far 151 pts have been enrolled. The study treatment includes two (OEPA; early stages), four (two cyclesof OEPA and two cycles of COPP/COPDAC), intermediate stages) or six (two cycles of OEPA and four cycles of COPP/COPDAC; 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: MRI 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 if overall FDG-PET scanning is negative 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 54% for early stages, 39% for intermediate and 27% for advanced stages determined by central review at the study office in Halle/Leipzig.

079 A MULTI-CENTRE STUDY OF THE TREATMENT AND CHARACTERISATION OF BURKITT LYMPHOMA IN 4 AFRICAN COUNTRIES

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Introduction: The use of intensive chemotherapy regimens hasimproved 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 INCTR. 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%), orbital 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/m^2, vincristine: 1.4 mg/m^2 and methotrexate (MTX): 75 mg/m^2, with thrice weekly intra-thecal (i/t) MTX+cytosine arabinoside (ara-C). 35 pts with refractory/recurrent disease received 4 cycles of ifosfamide: 1.5G/m^2 (with mesna), etoposide: 60mg/m^a and ara-C: 100mg/m^2, + 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%), CR:142, 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 ALCL – A BFM-GROUP ANALYSIS

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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 distribution of X-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 *TPM3-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 gene transcripts. *NPM-ALK* mRNA was detected in 55 of 63 ALK-positive tumors (87%) all 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 *TPM3-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 *TPM3-, TFG-, ATIC-, CLTC-* and *Myh9-ALK* fusion transcripts in the remaining 3 tumors. However, tumor material was not sufficient for 5′RACE. One ALCL showed nuclear and cytoplasmic ALK staining suggesting NPM-ALK fusion; however, an ALK-fusion gene could not be detected by RT-PCRs 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 ALCL99 RANDOMISED TRIAL

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Introduction: ALCL99 is a randomised trial for paediatric anaplastic large cell lymphoma based on the BFM protocol. Using a factorial design, comparison was made of two doses and schedules of Methotrexate (MTX) and testing the impact of adding vinblastine (VLB) 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 1 g/m^2 in 24 h with late rescue and with intrathecal MTX (IT) (MTX1) *vs* MTX 3 g/m^2 in 3h with early rescue, without IT (MTX3). Before 1st c B, Tt of high-risk pts was randomized with or without of VLB. Acute tox was assessed using CTC v2.

Results: Between 1999 and 2005, 352 pts from 175 centres were recruited. Tox assessed after 2050 induction c included: gr-4 haematological (haematol) tox after 72% c; infection 41%; gr3-4 SGOT/SGPT elevation 10%; gr3-4 stomatitis 13%. Weight gain >20% was seen in 19% pts. Four pts (1.1%) died of induction treatment-related toxicity. Stomatitis and liver tox was more frequent after c B. Haematol tox and infection was more frequent after c A. Tox: gr-4 haematol tox, infection and gr3-4 stomatitis was significantly more frequent after MTX1 than after MTX3 c (79% *vs* 64%; 50% *vs* 32%; 21% *vs* 6%). Tox rates did not differ between c with and without VLB.

Conclusions: High rate of acute tox must be kept in mind when using ALCL99 protocol. Chemotherapy including MTX 3 g/m^2 3h is less toxic than the regimen with MTX 1g/m^2 in 24h. The addition of VLB is not associated with an increased risk of toxicity.

082 MRD ANALYSIS IN MATURE B-ALL OF CHILDHOOD BY I_GGENE REARRANGEMENT AND LD-PCR

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Large-scale studies on minimal residual disease (MRD) in acute lymphoblastic leukemia (ALL) have shown that quantification of MRD levels is needed for reliable MRD-based risk group assignment. Recently, we have shown that MRD, studied by Long-Distance PCR (LD-PCR) for t(8;14), is a negative prognostic factor also in the less frequent mature B-cell ALL (B-ALL). However t(8;14) is detectable in about 70% of B-ALL, thus preventing analysis of MRD by this means in the remaining patients. The aim of our study was to evaluate the feasibility of real-time quantitative PCR (RQ-PCR) assay for detection ofpatient-specific immunoglobulin (Ig) gene rearrangements, according to the guidelines of European Study Group on MRD detection in ALL, and to compare the sensitivity of such a method with LD-PCR for t(8;14) in B-ALL. We studied a total of 39 B-ALL samples corresponding to different time points during BFM-based treatment: at diagnosis, before the second cycle of chemotherapy, at stop therapy. Eleven of 13 patients were positive at diagnosis by LD-PCR for t(8,14) and 9 of them became negative after the first chemotherapy cycle. Three patients turned positive at stop therapy and subsequently relapsed. The Ig gene rearrangement study gave the same results for all of the patients with a sensitivity of $10^{-4.}$ The two t(8;14) negative patients were positive for two Ig gene rearrangement markers and one maintained the molecular positivity during treatment. The preliminary results of our study suggest that the two methods have similar sensitivity. Because the assay for MRD studies should be simple, fast and relatively inexpensive, we would suggest to screen all B-ALL patients at diagnosis for t(8;14) by LD-PCR: in t(8;14) positive patients, MRD studies could be carried-out by using this approach, whereas in negative patients MRD could be assessed by using the clonotypic Ig gene rearrangements.

083 A STUDY OF RITUXIMAB AND IFOSFAMIDE, CARBOPLATIN, ETOPOSIDE (ICE) CHEMOTHERAPY IN CHILDREN WITH RECURRENT/REFRACTORY B-CELL NON-HODGKIN LYMPHOMA (NHL) AND MATURE B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL). A CHILDREN'S ONCOLOGY GROUP REPORT

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Background: Patients with relapsed/refractory B-cell NHL and B-ALL represent a significant challenge for retrieval. We sought to estimate the response rate and therapy related toxicities of rituximab combined with ICE chemotherapy in patients with relapsed and refractory B-cell NHL and mature B-ALL.

Methods: Patients received rituximab and ICE for 1 to 3 cycles, depending upon response. Rituximab (375 mg/m^2) was given on day 1 and 3 of each cycle (day 1 only for cycle 3), with ifosfamide (3000 mg/m^2) and etoposide (100 mg/m^2) given on days 3, 4, and 5 and carboplatin (635 mg/m^2) given on day 3 only. G-CSF support was given after each cycle.

Results: A total of 41 treatment courses were administered to the 20 eligible patients. Only one patient was removed from study due to prolonged myelosuppression. Grade 2-5 allergic reactions (fever, rash, chills, hypotension) associated with rituximab infusion were reported in 6 of the 41 treatment courses; all continued with therapy. Of the 6 eligible patients with diffuse large B-cell lymphoma, 3 achieved complete remission (CR), 1 had stable disease (SD), and 2 had progressive disease (PD). Of the 14 eligible patients with Burkitt lymphoma and B-ALL, there were 4 complete responses (CR), 5 partial responses (PR), 1 SD and 4 with PD. Thus the CR/PR rate for the entire group was 12/20 (60%, 95% CI 39%-81%). Overall survival was significantly greater in the responding patients (8 of 12, one with disease, f/u 13=30 mos,) vs. the non-responders (0 of 8, p=.0001). Six patients were able to proceed to consolidation with high-dose therapy and stem cell rescue (4 auto, 2 allo), with 5 survivors.

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 CHEMOIMMUNOTHERAPY (RITUXIMAB + FAB CHEMOTHERAPY) IN CHILDREN AND ADOLESCENTS WITH INTERMEDIATE RISK B-CELL NHL: A CHILDREN'S ONCOLOGY GROUP REPORT

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Introduction: Children with intermediate risk (St. Jude stage III/IV) B-NHL have an EFS ≥90% 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 ≥98% 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 B4 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/m^2/dose (generously supplied by Genentech) day -2 in

COPADM1 and Day 0 CYM 1 and 2 (sub-pilot) and day -2 and 0, COPADM 1 and 2 and day 0 CYM 1 and 2 (pilot).

Results: 48 children, median age 11 (1-23) yrs, 4/1 M/F, 59% BL, 24% DLBCL, 5% PMBL, 12% NOS,90/10% 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?

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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 entities 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 $\geq$ 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 $\leq$ 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.