session 6 – extranodal lymphoma

061 THE NF-κB PATHWAY COMPONENT A20 (TNFAIP3) IS COMMONLY INACTIVATED BY DNA MUTATIONS AND DELETIONS IN EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA (EMZL)

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Introduction: In EMZL, 3 recurrent translocations [t(11;18), t(1;14), t(14;18)] target the NF-kB pathway. These translocations have not been identified in nodal (NMZL) and splenic MZL (SMZL). Recently, 6q23 chromosomal deletions involving the A20 gene, a negative regulator of NF-kB, were reported in orbital EMZL (Honma et al, '08).

Aim: To further explore the role of A20 as a tumor suppressor in MZL subtypes by investigating its inactivation due to DNA mutations or deletions.

Material and Methods: 10 EMZL (2 skin, 3 parotid, 4 lung, 1 jejunum), 10 NMZLs and 12 SMZLs were studied. Metaphase spreads were analyzed by G-banding. FISH for CEP 3 and 18, MALT1, IAP2/MALT was performed. Genome-wide DNA profiles were obtained with Affymetrix GeneChip Human Mapping 250K arrays. All coding A20 exons and intron-exon junctions were sequenced.

Results: Overall, mutations were identified in 9/32 MZLs (28%): 7 heterozygous and 2 with a deletion of the other allele. Six frameshift mutations (deletions, insertions) were predicted to code for truncated A20 proteins. Six EMZL (60%) were mutated, with frameshift mutations in 3 (30%, 2 skin, 1 jejunum). One additional lung EMZL had an interstitial deletion of the A20 gene locus, uniparental disomy of the entire 6q and a mutation in exon 2, with alternative splicing. Two NMZL (20%) showed frameshift mutations, one also bearing a 6q23-qter deletion, encompassing the A20 gene locus. One frameshift mutation was detected in SMZL (8%). Further analysis of A20 by FISH is ongoing.

Conclusions: A20 mutations and/or deletions were detected in MZL, the vast majority were predicted to code for a truncated A20 protein. Mutations were more frequent in EMZL than in NMZL or SMZL. In cases with available karyotypes (17/32), A20 mutations were mutually exclusive with known cytogenetic aberrations activating NF-kB. A20 inactivation may represent a common alternative mechanism of constitutive NF-kB activation in EMZL.

062 LONG-TERM OUTCOME FOLLOWING RADIOTHERAPY IN LOCALIZED EXTRANODAL MALT LYMPHOMAS

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Purpose: We analyzed the long term outcomes in stage IE & IIE MALT Lymphomas treated with involved field radiotherapy (RT).

Methods: 192 patients (pts) with stage I (169) & II (23) MALT lymphomas were seen from 1989 to 2004. RT was a component of therapy in 166 pts (86.5%) (RT alone, 74% and combined modality, 12.5%). Remaining 13.5% pts had either surgery or antibiotic or chemotherapy alone. Outcomes analysis focuses on the 166 pts who received RT. The median age was 60 yrs (23-93). The F:M ratio was 2:1. Presenting sites: orbit 70, stomach 22, salivary gland 28, thyroid 21, other head & neck sites 7, lung 5, urinary bladder 4, skin & soft tissue 3, breast 4, other GI sites 1, meninges 1. Common RT doses were 25 Gy (46%) and 30 Gy (36%), median dose to non-orbital sites was 30 Gy. For orbital sites: median 25 Gy. The median F/U was 7.6 yrs (0.67-16.2).

Results: A CR/CRu was seen in 165 (99.4%) pts. At last F/U, 16 pts had died (3 due to lymphoma, 13 from unrelated causes). The 10-yr relapse free rate (RFR) and overall survival (OS) were 77% and 87% respectively. The 10-yr RFR was 95% for thyroid, 100% for stomach, 68% for salivary glands and 67% for orbit. For those who achieved CR, 31 (19%) relapsed (orbit 18/70, salivary glands 7/28, thyroid 1/21, stomach 0/22 and others 5/25). Relapse locations: contralateral paired organs 8 (orbit: 4, parotid: 4), local relapse 2, distant sites 18, both local/distant sites 3. Distant relapses were typically at unusual mucosal sites (eg. lung, soft tissues, CNS) and occasionally at distant nodal sites. 25/31 (81%) relapses occurred within 5 yrs (13/25 within 2 yrs) and only 6 pts relapsed beyond 5 yrs. Only 4 pts (11%) had transformation to DLBCL, 2 of whom died of lymphoma. The 5-yr OS following relapse was 79%.

Conclusions: Moderate dose RT achieves excellent local control in localized MALT lymphomas. Thyroid and gastric MALTs had significantly less risk of distant relapse. For other presenting sites, relapses were observed commonly in non-irradiated paired-organs or in various extranodal sites. Despite relapse of disease, the overall survival remains excellent and transformation to large cell lymphoma was infrequent.

063 RITUXIMAB® CHOP WITH CNS AND CONTRALATERAL TESTIS PROPHYLAXIS IMPROVES THE OUTCOME OF PRIMARY TESTICULAR LYMPHOMA (PTL): FINAL RESULTS OF IELSG10 STUDY

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Introduction: PTL has poor prognosis with 5-yr OS of 40-55% and frequent failures in contralateral testis, CNS and extranodal sites. The prospective phase II international trial (IELSG10 and Intergruppo Italiano Linfomi) for stage I or II PTL aimed to define standard treatment for PTL. This analysis provides the final results of the study.

Material and Methods: From June 2001 to December 2006, 53 pts with untreated stage I-II PTL were enrolled and treated with: standard doses RCHOP21 for 6-8 (in stage II pts with slow response) courses; intrathecal methotrexate (IT MTX) 15mg for 4 doses; 30Gy scrotal RT to the contralateral testis for all pts and 30-36Gy regional RT to lymph-nodes for stage II.

Results: median age 64 (22-79); 40 and 13 stage I/II; 4 with bilateral testicular involvement; 6 LDH > normal. All received RCHOP21. Fifty received adequate CNS prophylaxis (at least 4 IT MTX); 3 less than 4 because of toxicity. Scrotal RT was given to 48 pts; 5 did not perform it (3 refusals, 1 PD and 1 bilateral orchiectomy). Fifty-two pts (98%) were in CR and 1 progressed. With a median follow-up of 42 months, 3-yr OS and 3-yr PFS were: 86% (95% CI 72-94%) and 83% (95% CI 68-91%). Eight relapsed or progressed: 2 in nodal sites, 4 in extranodal +/- nodal and 2 in CNS (1 isolated meningeal and 1 meningeal + nodal). The actuarial risk of CNS relapse at 3-yr, considering competitive risk of death, was only 2% (95% CI 0-5%). No contralateral testis relapses occurred. Nine pts died: 4 of DLBCL, 1 of colon carcinoma and 2 of AML 4 while in CR. Grade 3-4 toxicities were: leukopenia 27% and neurologic 13%. Infections were recorded in only 2 pts with no other extrahematological toxicities. No toxic deaths occurred.

Conclusions: RCHOP21 with complete CNS and scrotal prophylaxis improves the outcome of PTL compared with literature data. Contralateral testis relapses were not observed and the incidence of CNS relapse was low.

064 MENINGEAL DISSEMINATION (MD) IN PRIMARY CNS LYMPHOMA (PCNSL)

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We present the first prospective comparison of the diagnostic value of cerebrospinal fluid (CSF) cytomorphology, PCR of the rearranged immunoglobulin heavy-chain (IgH) genes, and magnetic resonance imaging (MRI) in conjunction with cell count and protein concentration for the detection of MD in immunocompetent PCNSL patients. A total of 282 immunocompetent PCNSL patients were evaluated for the presence of MD: 205 with CSF cytomorphology, 171 with PCR of the rearranged IgH CDRIII region genes in CSF and 217 with cranial MRI. MD was found in 33 patients (16%) by cytomorphologic examination, in 19 (11%) patients evaluated by PCR and in 8 (4%) patients by MRI. The incidence of MD was 17.4% (49 of 282 patients) considering either of these methods. Of cytomorphologically positive samples, lymphoma cells were confirmed by PCR in 32% only, whereas polyclonal B-cells were found in 58%. Conversely, of samples with monoclonal B-cells, only 35% were recognized cytomorphologically, whereas 59% were not. On the other hand, 74% of samples without a monoclonal PCR product were diagnosed as cytomorphologically negative, whereas in 12% lymphoma cells were seen. The probability of MD detection was higher in cases with CSF pleocytosis with an odds ratio (OR) of 2.48 (95% CI 1.15 -5.34, p=0.018), whereas CSF protein had no predictive value for MD detection. A relatively low incidence of MD in PCNSL was found in this study. The rate of discordant cytomorphology and PCR results was high. CSF pleocytosis had predictive value for MD detection. According to our findings, cytomorphologic results in CSF of

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PCNSL patients should be interpreted with caution and, when possible, verified by a more specific method like PCR.

065 RANDOMIZED PHASE II TRIAL ON PRIMARY CHEMOTHERAPY (CHT) WITH HIGH-DOSE METHOTREXATE (MTX) ALONE OR ASSOCIATED WITH HIGH-DOSE CYTARABINE (ARAC) FOR PATIENTS (PTS) WITH PRIMARY CNS LYMPHOMA (PCNSL)

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Background: MTX-based CHT is the conventional approach to PCNSL, but superiority of polyCHT over MTX alone is unproven. A benefit of adding araC to MTX has been suggested by a meta-analysis and a large retrospective series.

Patients: PCNSL pts (HIV-; 18-75 ys; PS≤3; 2004-2007) were randomized to receive 4 courses (interval 3 weeks) of MTX 3.5 g/mq (arm M) or MTX (same dose) + araC 2 g/mq x 2/d, d 2-3 (arm MA). CHT was followed by radiotherapy (RT). Pts were stratified based on IELSG score and centre RT policy for pts >60 ys in complete remission (CR) after CHT. CR rate (CRR) after CHT was the primary endpoint; planned accrual (α=0.05 β=0.2) for P_0 30% and P_1 50% was 39 pts/arm.

Results: 79 pts (median age 58 ys) were randomized to receive M (N=40) or MA (N=39). IELSG risk was low in 22 (28%) pts, intermediate in 48 (61%) and high in 9 (11%). Sixty-nine pts (87%) had a DLBCL. Ocular and meningeal disease were detected in 14% and 7% of cases, respectively. No differences in pts' characteristics between arms were observed. 231 (73%) of the 316 planned courses were actually delivered (M 71%; MA 76%). CHT was interrupted due to progressive disease in 20 (50%) M pts and 8 (21%) MA pts (p<0.001), toxicity in 1 (3%) M pt and 7 (18%) MA pts (p=0.009) and refusal in 2 MA pts. ≥25% dose reduction was indicated in 1 M pt and 17 MA pts. G4 neutropenia (10% vs. 74%), G4 thrombocytopenia (5% vs. 64%) and infections (3% vs. 23%) were more common in MA arm. All G3-4 non-hematological toxicity rates were <5%. One M pt (3%, cardiotoxicity) and 3 MA pts (8%, sepsis - hepatotoxicity) died of toxicity. Response after CHT was CR in 7 M pts and 18 MA pts (CRR: 18% vs. 46%; p=0.0002) and partial in 10 M and 9 MA pts (ORR 43% vs. 69%; p=0.0002). After CHT-RT, 11 M pts and 25 MA pts achieved CR (28% vs. 64%; p<0.0001). At a median f-up of 16 mo, 29 M pts and 22 MA pts experienced failure (PD, relapse, death), with a 3-yr EFS of 24% vs. 35% (p=0.02).

Conclusions: This is the first randomized trial on PCNSL with completed accrual. The addition of araC to MTX was associated with significantly better outcome and acceptable toxicity. MTX+araC may be the control arm for future randomized trials.

066 HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM-CELL TRANSPLANTATION AS FIRSTLINE TREATMENT OF PRIMARY CNS LYMPHOMA IN PATIENTS < 65 YEARS - UPDATED RESULTS FROM A PILOT AND PHASE II STUDY

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Introduction: Dose-intensified chemotherapy (HDT) and autologous stem-cell transplantation (ASCT) demonstrated high efficacy in the treatment of newly-diagnosed primary CNS lymphoma (PCNSL) in younger patients (pts.). A 5-year overall survival probability (OS) of 69% could be demonstrated in 30 pts within a phase-II trial on HDT and ASCT with consolidating whole-brain-irradiation (WBRT) (Illerhaus et al. JCO 2006). A subsequent pilot trial on HDT and ASCT without WBRT showed a 5-year OS of 77% (Illerhaus et al. Haematologica 2008). Here we give an update of our two different treatment regimens and future perspectives.

Patients and Methods: Thirty pts. ≤65 years were treated within the phase II trial, chemotherapy (CHT) consisted of 3 cycles of high-dose methotrexate (MTX, 8 g/m^2), 1 cycle of AraC (2x 3 g/m^2) plus thiotepa (TT, 40 mg/m^2) followed by rG-CSF and stem-cell-mobilization. Conditioning regimen included BCNU (400 mg/m^2) and TT (2x5 mg/kgBW) followed by ASCT. Hyperfractionated WBRT (45 Gy, 2x1Gy/d) was administered as consolidation. In our subsequent pilot trial 13 pts. (age 38-67 years) were treated without consolidating WBRT; CHT was intensified with 4 cycles MTX 8 g/m^2, 2 cycles AraC (2x 3 g/m^2) and TT (40 mg/m^2). Dose escalated HDT included BCNU (400 mg/m^2) and TT (4x5 mg/kgBW) followed by ASCT. WBRT was reserved for pts not responding to CHT.

Results: Median follow-up of the 30 pts treated within our phase II trial was extended to 95 months (mo), the updated 5-year OS of all pts is 66.6% and 82,3% of the subgroup of pts who underwent HDT and ASCT (n=23). Three additional deaths occurred due to relapse (n=2) after 45 and 71 mo and due to comorbidity (n=1) after 103 mo. Five of 30 pts developed severe leukoencephalopathy during follow-up. With a median follow-up of 35 mo in the 13 pts treated within the pilot-phase without consolidating WBRT 3 year OS of all pts is 77%. No further relapse or non-relapse mortality occurred in this pilot-group during. Most recent follow-up data will be presented in detail.

Conclusion: Sequential systemic application of high-dose cytostatic agents followed by HDT+ASCT is highly effective as initial therapy for pts with PCNSL. The restriction of WBRT to refractory disease shows similar OS rates and a decrease in neurotoxicity. In an ongoing multicenter phase-II trial immunotherapy with rituximab is combined with HDT and ASCT to further increase remission rates. A future randomised trial should be focused on the efficacy of consolidation with HDT supported by ASCT.

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