''Focus on...'' session: primary CNS lymphoma

031 IMPACT OF MENINGEAL DISSEMINATION (MD) ON OUTCOME IN PRIMARY CNS LYMPHOMA IN THE G-PCNSL-SG1 TRIAL

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Background: The prognostic impact of MD in PCNSL is still debated. Within the framework of a multicenter randomized trial (G-PCNSL-SG1) we evaluated patients for outcome according to the presence of MD.

Methods: Immunocompetent adult patients were initially treated with up to six cycles of high-dose methotrexate (HD-MTX; 4g/m^2) based chemotherapy without intrathecal therapy. Those randomized to radiotherapy subsequently received whole-brain radiotherapy (WBRT) with 45 Gy, in 1.5 Gy fractions; those randomized to chemotherapy did not receive further therapy in case of complete remission or high-dose cytarabine when complete response was not achieved. MD was defined by the presence of lymphoma cells in the cerebrospinal fluid (CSF) detected by at least one of the following methods: cytomorphology, detection of clonal B cells by polymerase chain reaction of rearranged immunoglobulin heavy-chain genes (IgH-PCR) or contrast enhancement of the leptomeninges on MRI.

Results: All 526 patients fulfilling the eligibility criteria were entered into the analysis. MD at presentation was detected in 104 (19.8 %) patients: 95 by cytomorphology, 16 by PCR and 17 by MRI. Pretherapeutic characteristics including age, Karnofsky performance score, sex, serum lactate dehydrogenase, lymphoma localization, mode of biopsy, histology, CSF protein elevation (>45mg/dl) and ocular involvement did not significantly differ in patients with MD and other patients (all p>0.05). Only CSF pleocytosis (>5/µl) was significantly more frequent in patients with MD (37 vs. 14%, p<0.001). The type of chemotherapy (HD-MTX: 83 vs. 75%, HD-MTX and ifosfamide: 17 vs. 25%) applied and the frequency of WBRT (39 vs. 34%) were not significantly different in the group with and without MD. Median overall survival (OAS) in the MD group was 21.5 (95% CI 17.1-25.8) months as compared to 22.4 (17.3-27.5) months in other patients (p=0.8); median progression free survival (PFS) was 6.1 (1.6-10.5) and 7.0 (5.2-8.8) months, respectively (p=0.9). Median OAS and PFS were not significantly different in patients with elevated CSF protein or CSF pleocytosis compared to patients with normal CSF values.

Conclusion: MD, elevated CSF protein and CSF pleocytosis had no impact on outcome in this trial.

032 IS PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL) REALLY RESTRICTED TO THE CNS? EVALUATION OF SUBCLINICAL SYSTEMIC INVOLVEMENT WITH PCR

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Introduction: The strong affinity of PCNSL to the CNS is not fully understood. It was hypothesized that occult systemic disease may be present in PCNSL and act as a reservoir of malignant cells for relapse.

Methods: We examined bone marrow (BM), peripheral blood (pB) and tumor of 62 immunocompetent patients with newly diagnosed and relapsed PCNSL using PCR for the presence of clonally rearranged immunoglobulin heavy chain genes. To all samples (50 ng DNA), three different framework region (FR) primer sets (FR1, FR2 and FR3) were applied in conjunction with a heavy chain joining segment (JH) consensus primer (JH22). Baseline routine staging procedures were negative for systemic lymphoma in all patients.

Results: A dominant PCR amplificate was found in pB and/or BM of 15 (24%) patients. In 3 (5%) patients, identical dominant PCR products were detected in PCNSL tissue, BM and/or pB, indicating that the same tumor cell population was present in and outside the CNS. In one patient with identical dominant PCR amplificates in pB, BM and CNS, follow-up PCR showed a persistent monoclonal amplificate in pB 24 months after diagnosis despite complete remission on cranial MRI and no evidence of systemic disease. In the same patient, a lymphoma relapse in the gastrointestinal tract 5 years after diagnosis showed a different dominant PCR product. The second patient with the same dominant amplificates in CNS, pB and BM relapsed in the CNS 12 months after diagnosis and responded to whole-brain radiation, but died of pulmonary embolism before follow-up PCR could be performed. The third patient evidenced dominant PCR products in pB 3 years after diagnosis of PCNSL and in complete remission. The PCR products were identical to those in tumor tissue and cerebrospinal fluid at initial diagnosis. Three (5%) additional patients had dominant amplificates in pB or BM different from the PCNSL tissue specimen that might represent reactive B-cell clones. In 9 (15%) patients, dominant PCR products were found in pB and/or BM, but brain tumor specimens did not contain enough material for PCR analysis or have not yet been analyzed. One patient without detection of monoclonal amplificates in pB or BM relapsed in the breast.

Conclusions: Subclinical systemic disease is traceable in a substantial percentage of patients with PCNSL. It can persist for years, and, under conditions remaining to be defined, cause both CNS and systemic relapses.

033 HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM-CELL TRANSPLANTATION AS FIRST-LINE TREATMENT FOR PRIMARY CNS LYMPHOMA - UPDATED RESULTS OF A PILOT AND PHASE II STUDY

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Introduction: High-dose 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.). We reported a 5-year overall survival probability (OS) of 69% d 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 restricting WBRT to patients not in complete remission after HDT showed a 5-year OS of 77% (Illerhaus et al. Haematologica 2008). Here we give an update of our two different treatment regimens.

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 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 8g/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.

Results: Median follow-up of the 30 pts treated within our phase II trial was extended to 125 months (mo, range 2 - 149), the updated 5-year OS of all pts is 66.7% and 82,6% of the subgroup of pts who underwent HDT (n=23). Five additional deaths occurred due to relapse (n=3) after 45, 71 and 139 mo, due to comorbidity (n=1) after 103 mo and due to gastric cancer after 121 mo (n=1). The median survival of all pts treated with HDT and ASCT was 103 mo and 139 mo, respectively. Five of 30 pts developed severe leukoencephalopathy during follow-up. With a median follow-up of 69 mo (range 2 - 94) in the 13 pts treated within the pilot-phase without consolidating WBRT 5 year OS of all pts is 77%. During follow-up two pts developed severe leukencephalopathy, one patient died of multiple cerebral infarctions. Most recent follow-up data will be presented in detail.

Conclusion: High-dose chemotherapy (HDT) and autologous stem-cell transplantation is highly effective as initial therapy for pts with PCNSL. The restriction of WBRT to patients not in CR after HDT shows similar OS rates. In an ongoing multicenter phase-II trial rituximab is combined with HDT and ASCT to further increase remission rates.

034 IMMUNOCHEMOTHERAPY WITH INTENSIVE CONSOLIDATION, WITHOUT BRAIN IRRADIATION, FOR PRIMARY CNS LYMPHOMA: A PILOT STUDY WITH PROGNOSTIC ASSESSMENT BY DIFFUSION-WEIGHTED MRI

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Introduction/Background: We evaluated a novel induction for primary central nervous system lymphoma (PCNSL) that includes immunochemotherapy with

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methotrexate, temozolomide and rituximab (MT-R) followed by intensive consolidation with high-dose etoposide and cytarabine (EA), without whole brain irradiation. The prognostic utility of minimum apparent diffusion coefficient (ADCmin) values derived from diffusion-weighted magnetic resonance imaging (DW-MRI) of untreated PCNSL tumors was evaluated for this regimen.

Materials and Methods: Thirty-one patients (median age, 61; median KPS, 60) received induction therapy with methotrexate 8 gm/m2 every 14 days for 8 cycles. Rituximab was given day 3 of the first 6 cycles. Temozolomide 150 mg/m2 was administered days 7 to 11 of odd-numbered cycles. Patients with responsive or stable CNS disease received consolidation with etoposide 40 mg/kg over 96 hours plus cytarabine 2 gm/m2 every 12 hours for eight doses. Standard MR imaging of the brain without and with intravenous contrast was performed including DW-MRI using b factor of 1000 s/mm2. ADCmin of the contrast-enhancing tumor was determined from DW-MRI.

Results: The complete response rate for MT-R induction was 51%. At a median follow-up of 61 months, 2-year progression-free and overall survival was 45% and 58%, respectively. For patients receiving EA consolidation, the 2-year progression-free and overall survival was 78% and 93%, respectively. EA consolidation was also effective in a subgroup of patients who presented with CNS lymphoma with concomitant systemic disease. Tumor ADCmin < 384 x 10-6 mm2/s was significantly associated with increased risk of progression and shorter survival.

Conclusions: MT-R induction was effective and well-tolerated. EA consolidation resulted in long-term progression-free and overall survival comparable to whole-brain radiotherapy, without evidence of neurotoxicity. These promising results are the basis for a multicenter study through CALGB which is evaluating the response rate, toxicity and long-term efficacy of the MTR-EA regimen in PCNSL. Tumor ADCmin was a more accurate prognostic biomarker for PCNSL patients treated with the MTR-EA regimen than risk scores based upon established clinical variables.

035 INTENSIVE CHEMOTHERAPY WITH THIOTEPA, BUSULFAN, AND CYCLOPHOSPHAMIDE (TT-BU-CY) WITH HEMATOPOIETIC STEM CELL RESCUE (IC + HCR) IN RELAPSED OR REFRACTORY PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL) OR INTRAOCULAR LYMPHOMA (IOL): A RETROSPECTIVE STUDY OF 74 CASES

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Introduction: In relapse or refractory PCNSL patients under 65, the most promising therapeutic strategy consists of salvage treatment followed by IC + HCR.

Methods: We conducted a retrospective analysis of patients who received IC + HCR with TT-Bu-Cy for a relapse or refractory PCNSL or IOL.

Results: Seventy-four patients were identified. Median age was 56 (range, 23-67). After first-line treatment, 44 patients had relapsed. Ten patients were in PR, and twenty patients had a refractory disease. After salvage treatment and before IC + HCR, patients were in CR (n = 31), in PR (n=24), in SD (n=2), or in PD (n=17). Disease status after IC + HCR was not evaluable in 4 cases. The best observed response was a CR in 61 patients, PR in 3 patients, SD in 2 patients, and a PD in 4. With a median follow up for surviving patients of 52 months, the probability of 2 years OS was 70.4 % [60.5; 81.9]. When patients with an isolated IOL (n=14) were excluded, median OS for chemosensitive (CR + PR) and chemoresistant disease (SD + PD) at time of IC + HCR was 97.1 (36.43-NA) and 18.5 (7.34-NA) months respectively (pvalue=0.017).

Conclusion: Chemosensitive patients at relapse have a very favorable outcome after IC + HCR with TT-Bu-Cy. Details of results according to subgroups of patients will be presented.

036 LONG-TERM COGNITIVE OUTCOME IN PATIENTS WITH PRIMARY CNS LYMPHOMA (PCNSL): A TRANS-ATLANTIC MULTI-CENTER STUDY

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Introduction: Delayed treatment-related neurotoxicity in primary CNS lymphoma (PCNSL) is a significant problem especially since improved treatments have increased survival rates. The study purpose is to describe neuropsychological and neuroimaging outcomes in PCNSL patients (pts) in complete remission (CR) and to correlate neuropsychological and imaging indicators of neurotoxicity.

Methods: Four centers in Germany and U.S. collaborated. Patients in CR for 2 yrs or more were evaluated with a standardized neuropsychological test battery and brain MRI. The battery was developed for prospective trials and evaluates attention, processing speed, motor skills, verbal memory, verbal intelligence, and quality of life (Correa D et al, 2007).

Results: Demographic and treatment data on 78 pts (41M/37F) are summarized. At initial presentation, median age was 59 yrs; median KPS was 80; brain parenchyma disease was present in 73 pts; 6 pts had positive or atypical CSF for lymphoma cells; and 2 pts had ocular involvement. Treatment modalities and the number of pts treated with each are summarized in the Table:

Treatment	No. of pts
High-dose methotrexate (HD MTX)-based chemotherapy (CHT) alone	31
MTX-based intra-arterial CHT with blood-brain barrier disruption alone	25
HD MTX-based CHT followed by HDT/autologous stem cell transplantation (ASCT) alone	8
HD MTX-based CHT and WBRT	9
HD MTX-based CHT followed by HDT/ASCT and WBRT	5

Median follow-up from diagnosis to testing is 5.6 yrs (min 2, max 26 yrs). Neuropsychological data will be available for presentation. Number of pts with white matter MR abnormalities and whether abnormalities correlate with neuropsychological outcomes will be reported.

Conclusions: This is the largest series of PCNSL pts in CR with the longest median follow-up to undergo prospective neuropsychological testing with a standardized battery, thus providing a unique comparison series for future PCNSL trials.

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