“Focus on…” session: primary CNS lymphoma

031 IMPACT OF MENINGEAL DISSEMINATION (MD) ON OUTCOME IN PRIMARY CNS LYMPHOMA IN THE G-P CNSL-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-P CNSL-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/m²) 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: cytology, 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, 17 by PCR and 16 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 (>5cells/μl) was significantly more frequent in patients with MD (57 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 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 SILENT? IMPACT 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 ml), three different framework regions (FR) primer sets (FR1, FR2 and FR3) were added 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 amplicate 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 amplicates in pB, BM and CNS, follow-up PCR showed a persistent monoclonal amplicate 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 amplicates 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 amplicates 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% in 30 pts within a phase-II trial on HDT and ASCT with consolidating whole-brain irradiation (WBRT) (Ilmerhaus 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% (Ilmerhaus et al. Haematologica 2008). Here we give an update of our two different treatment regimens.

Patients and Methods: Thirty pts. <65 yrs were treated within the phase II trial, chemotherapy (CHT) consisted of 5 cycles of high-dose methotrexate (MTX, 8 g/m²), 1 cycle of AraC (2x 3 g/m²) plus thiopeta (TT, 40 mg/m²) followed by rG-CSF and stem-cell mobilization. Conditioning regimen included BCNU (400 mg/m²) and TT (2x5 mg/kgBW) followed by ASCT. Hyperfractionated WBRT was administered as consolidation. In our subsequent pilot trial 13 pts. (age 38-67 yrs) were treated without consolidating WBRT; CHT was intensified with 4 cycles MTX 8g/m², 2 cycles AraC (2x 3 g/m²) and TT (40 mg/m²). Dose escalated HDT included BCNU (400 mg/m²) 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 leukoencephalopathy, 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 immunochemothrapy with
INTRAOCULAR LYMPHOMA (IOL): A RETROSPECTIVE STUDY OF 74 PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL) OR therapeutic strategy consists of salvage treatment followed by IC.

Introduction: In relapse or refractory PCNSL patients under 65, the most promising 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, we conducted a retrospective analysis of patients who received 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 occult involvement. Treatment modalities and the number of pts treated with each are summarized in the Table:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of pts</th>
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<tbody>
<tr>
<td>High-dose methotrexate (HD MTX)-based chemotherapy (CHT) alone</td>
<td>31</td>
</tr>
<tr>
<td>HD MTX-based intra-arterial CHT with blood-brain barrier disruption alone</td>
<td>25</td>
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<tr>
<td>HD MTX-based CHT followed by HDTI</td>
<td>8</td>
</tr>
<tr>
<td>HD MTX-based CHT and WBRT</td>
<td>9</td>
</tr>
<tr>
<td>HD MTX-based CHT followed by HDTI and WBRT</td>
<td>5</td>
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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.