RANDOMIZED PHASE II TRIAL ON PRIMARY CHEMOTHERAPY WITH HIGH-DOSE METHOTREXATE ALONE OR ASSOCIATED WITH HIGH-DOSE CYTARABINE FOR PATIENTS WITH PRIMARY CNS LYMPHOMA (IELSG #20 TRIAL): TOLERABILITY, ACTIVITY AND EVENT-FREE SURVIVAL ANALYSIS
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Background
High-dose methotrexate (HD-MTX)-based chemotherapy is the conventional approach to primary CNS lymphomas (PCNSL), but superiority of polychemotherapy over HD-MTX alone is unproven. A benefit of adding high-dose cytarabine (araC) to MTX has been suggested by a meta-analysis and a large retrospective series. This is a randomized phase II trial comparing HD-MTX monochemotherapy versus HD-MTX plus HD-araC as primary chemotherapy in immunocompetent patients (pts) with PCNSL.

Patients
HIV-negative pts with newly diagnosed PCNSL, age 18-75 ys, ECOG-PS ≤3, and measurable disease were randomly assigned to receive 4 courses (interval 3 weeks) of MTX 3.5 g/mq (control arm) or MTX (same dose) + araC 2 g/mq x 2/d, d 2-3 (experimental arm). Chemotherapy was followed by complementary whole-brain irradiation (WBRT). Pts were stratified based on IELSG score and centre WBRT policy for pts >60 ys in complete remission (CR) after chemotherapy. Complete remission rate (CRR) after chemotherapy was the primary endpoint; planned accrual (a=.05 b=.2) for P0 30% and P1 50% was 39 pts/arm.

Results
79 pts (median age 58 ys; range 25-74) were randomly assigned to receive MTX (n=40) or MTX+araC (n=39). IELSG risk was low in 22 (28%) pts, intermediate in 48 (61%) and high in 9; 7 (9%) pts had ocular lesions and 7 (9%) had meningeal disease; no differences in clinical presentation between arms were observed.

Two hundred thirty-one (73%) of the 316 planned courses were actually delivered (MTX 71%; MTX+araC 76%). Causes of chemotherapy interruption were: progressive disease (PD) in 20 (50%) MTX and 8 (21%) MTX+araC pts (p<0.001); toxicity in 1 (3%) MTX and 7 (18%) MTX+araC pts (p=0.009) and refusal in 2 MTX+araC pts. Dose reduction ≥25% was indicated in 1 MTX and 17 MTX+araC pts. G4 neutropenia (10% vs. 74%), G4 thrombocytopenia (5% vs. 64%) and infections (3% vs. 23%) were significantly higher in MTX+araC arm. All G3-4 non-hematological toxicities were <5%. One MTX pt (3%, cardiotoxicity) and 3 MTX+araC pts (8%, sepsis - hepatotoxicity) died of toxicity.

After chemotherapy, 7 MTX and 18 MTX+araC pts achieved CR (18% vs. 46%; p=0.0002); 9 MTX and 9 MTX+araC pts achieved PR (ORR: 40% vs. 69%; p=0.0002). After conclusion of the whole upfront treatment, 11 MTX and 25 MTX+araC pts achieved CR (28% vs. 64%; p<0.0001). At a median follow-up of 25 months, 31 MTX and 22 MTX+araC pts experienced failure (PD, relapse, death), with a 3-yr event-free survival (EFS) of 20% and 38% (p=0.01), respectively. Relapse/progression involved the brain, alone (n=34) or associated with eyes or meninges (n=8) in 42 (88%) of relapses cases, while it involved meninges, with or without eyes, in 4 (8%) cases; a systemic dissemination was detected in 2 (4%) pts. No differences in relapse sites between treatment arms were observed. Salvage with MTX+araC in 6 pts relapsed after MTX was invariably followed by PD. Conversely, 8 of 12 pts with PD after primary chemotherapy treated with salvage WBRT achieved an objective response, with a median response duration of 10 months (1-51+).

Treatment arm and IELSG risk score were the two variables independently associated with EFS. Fifteen MTX and 21 MTX+araC pts are alive, with a 3-yr OS of 34% vs. 47% (p=0.12).

Conclusions
This is the first randomized trial on PCNSL with completed accrual. The addition of HD-araC to HD-MTX resulted in significantly better outcome and acceptable toxicity. MTX+araC may be the chemotherapy combination used as control arm in future randomized trials.