

# **Effects on Survival of Non-Myeloablative Chemoimmunotherapy Compared to High-Dose Chemotherapy Followed By Autologous Stem Cell Transplantation (HDC-ASCT) As Consolidation Therapy in Patients with Primary CNS Lymphoma - Results of an International Randomized Phase III Trial (MATRix/IELSG43)**

Gerald Illerhaus, MD, Andrés J.M. Ferreri, MD, Mascha Binder, MD, Peter Borchmann, Justin Hasenkamp, MD, Stephan Stilgenbauer, MD, Alexander Roeth, MD<sup>7</sup>, Thomas Weber<sup>8\*</sup>, Gerlinde Egerer, MD<sup>9\*</sup>, Thomas Ernst, MD, Bernd Hertenstein, MD, Georg Lenz, MD, Guido Kobbe, MD, Uta Brunnberg, Christian Schmidt, MD, Michael Kneba, MD, PhD, Martin Dreyling, MD, Robert Möhle, MD, Jens Panse, MD, Thomas Heinicke, MD, Sebastian Schroll, MD, Thomas S. Larsen, MD, PhD, Hans Salwender, MD, Ralph Naumann, MD, Georg Hess, MD, Lorenz Thurner, MD, Tobias Pukrop, MD, Ulrich Keller, Anne Kirsti Blystad, MD, Frank P. Kroschinsky, MD, Francesca Re, MD, Elisa Pulczynski, MD, Lorella Orsucci, MD, Lisa Pospiech, Martina Deckert, Maurilio Ponzoni, MD, Julia Wendler, MD, Elke Valk, PhD, Teresa Calimeri, MD, PhD, Benjamin Kasenda, MD PhD, Martin Trepel, MD, Heidi Fricker, Philipp von Gottberg, Elvira Burger, Gabriele Ihorst, Olga Grishina, Claudia Hader, MD, Emanuele Zucca, MD, Jürgen Finke, MD, PhD and Elisabeth Schorb

**BACKGROUND:** Patients with primary central nervous system lymphoma (PCNSL) eligible for intensive treatment approaches are currently treated with high-dose methotrexate (HD-MTX) based induction immuno- chemotherapy followed by consolidative high-dose chemotherapy and ASCT (HDC-ASCT). However, it is unclear whether overcoming chemo- resistance and subsequently eliminating minimal residual disease may also be achieved by conventional-dose non-myeloablative immuno- chemotherapy, comprising non-cross resistant cytotoxic agents able to cross the brain-blood-barrier. We thus conducted an international randomized phase III trial comparing HDC-ASCT with non-myeloablative consolidation in patients with newly diagnosed PCNSL (MATRix/IELSG43 trial, NCT02531841). This is the first report on its primary endpoint.

**METHODS:** This open label, randomized phase III trial was conducted in 56 centers of 5 countries (Germany, Italy, Denmark, Norway, Switzerland).

Main eligibility criteria included newly diagnosed PCNSL, HIV-negative, age 18-65 years irrespective of ECOG PS or 66-70 years with ECOG PS  $\leq 2$ , and adequate organ function. Induction consisted of 4 cycles of MATRix regimen (rituximab 375 mg/m<sup>2</sup>/d days 0 & 5; methotrexate 3.5 g/m<sup>2</sup> day 1; cytarabine 2 × 2 g/m<sup>2</sup>/d days 2 & 3; thiotepa 30 mg/m<sup>2</sup> day 4, every 21 days). Stem cell harvest was conducted after the 2nd cycle. Pts achieving at least partial response (PR) after completion of induction were randomly allocated to either arm A with two courses of R-DeVIC regimen (375 mg/m<sup>2</sup> day 0; dexamethasone 40 mg/d days 1 to 3; etoposide 100 mg/m<sup>2</sup>/d days 1 to 3; ifosfamide 1500 mg/m<sup>2</sup>/d days 1 to 3; carboplatin 300 mg/m<sup>2</sup> day 1); or arm B, consisting of HDC with BCNU 400 mg/m<sup>2</sup> (day-6) and thiotepa 2 × 5 mg/kg/d days -5 & -4) followed by ASCT. The primary endpoint progression-free survival (PFS) was analyzed with a Cox proportional hazards model, containing the randomized treatment as hypothesis variable and the stratification variable response status as a covariate.

**RESULTS:** Between July 2014 and August 2019, 368 pts were registered; 346 started treatment, 260 (75%) completed the induction therapy, and 115 and 114 pts were randomly assigned to arm A and arm B, respectively. Main reasons for not reaching randomization were toxicities (n= 87; 25%) and disease progression (n= 36; 10%). Median age of the randomized pts was 59 years (range 21 – 70) with 22.3% of pts being 65 years or older. Distribution of patient characteristics were well balanced between arms. Median follow-up of all registered patients is 44 months (range 0,2-86). 239 of 346 (69%) pts responded to induction treatment, 27% achieved a complete remission (CR) and 52% a partial remission (PR). Both consolidation strategies were well tolerated: R-DeVIC and HDC-ASCT were completed in 100 (87%) and 111 (97%) pts, respectively. 13 (3.8%) pts died of treatment-related complications during induction treatment, 11 of them due to neutropenic infectious complications. Consolidation treatment with R-DeVIC or HDC-ASCT resulted in a substantial increase of pts with CR (65% in arm A and 68% in arm B, respectively; p= 0.71). To date, there were 79 PFS events: 67 pts experienced progressive disease after randomization (47 for arm A and 20 for arm B). 6 pts died of toxicity during consolidation treatment (2 arm A and 4 arm B), and 6 pts died of unrelated causes while relapse-free (5 arm A and 1 arm B). The 3-year PFS (primary endpoint) differed significantly between the two arms: 79% (95% CI 71-86) after HDC-ASCT and 53% (95% CI 43-62%) after R-DeVIC (HR 0.42; p=0.0003). The 3-year OS was 86% (95% CI 78-91) for HDC-ASCT arm and 71% (95% CI 61-78) for R-DeVIC arm (HR 0.47; p=0.01). The evaluation of neurocognitive functions showed no difference between arms. **CONCLUSION:** This international randomized phase III trial demonstrates that consolidation with HDC-ASCT results in significantly better outcome than non-myeloablative chemoimmunotherapy. This comes along without any measurable negative effect on neurocognitive functions and with an excellent risk-to-benefit ratio. HDC-ASCT is the standard consolidation therapy for fit PCNSL patients.

### **Kurz zusammengefasst.**

- Größte randomisierte Phase-III Studie zum Vergleich der Hochdosischemotherapie und Stammzelltransplantation gegenüber der konventionellen Chemotherapie bei Patienten mit primären ZNS-Lymphomen bis 70 Jahre.
- Die Studie erbrachte einen hochsignifikanten Vorteil hinsichtlich des Krankheitsfreien und des Gesamtüberlebens durch die Hochdosis Chemotherapie gegenüber der konventionellen Chemotherapie. Zahlen siehe Text
- Das Risiko an einem Lymphom zu Versterben konnte durch die Hochdosis Chemotherapie um 54 % reduziert werden.

