Induction Chemo-Immunotherapy with the Matrix Regimen in Patients with Newly Diagnosed PCNSL - a Multicenter Retrospective Analysis on Feasibility and Effectiveness in Routine Clinical Practice

Document Version
Final published version

Link to publication record in Manchester Research Explorer

Citation for published version (APA):

Published in:
Blood

Citing this paper
Please note that where the full-text provided on Manchester Research Explorer is the Author Accepted Manuscript or Proof version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version.

General rights
Copyright and moral rights for the publications made accessible in the Research Explorer are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Takedown policy
If you believe that this document breaches copyright please refer to the University of Manchester’s Takedown Procedures [http://man.ac.uk/04Y6Bo] or contact uml.scholarlycommunications@manchester.ac.uk providing relevant details, so we can investigate your claim.
Abstract

Background

The randomized IELSG32 trial compared 3 different induction chemo(immuno)therapy combinations in patients with newly diagnosed primary CNS lymphoma (PCNSL). Results showed that the MATRix combination (methotrexate [MTX], cytarabine [AraC], thiopeta, and rituximab) followed by consolidation therapy significantly improved outcomes in patients up to the age of 70 years (Ferreri et al. Lancet Haematol 2016; Ferreri et al. ASH abstract 2016). The MATRix protocol (4 cycles repeated every 3 weeks) followed by consolidation high dose chemotherapy and autologous stem cell transplant (HDT–ASCT) or whole–brain radiotherapy (WBRT) is now widely regarded as a new treatment standard and benchmark for future randomized trials. However, treatment associated toxicity is common, and many patients encountered in routine practice are older/frailer than those treated in the IELSG32 trial. We conducted a retrospective multicenter
study of clinical outcomes in newly diagnosed PCNSL patients treated with MATRix in routine clinical care.

**Methods**

This retrospective cohort included all consecutive patients with newly diagnosed PCNSL who received at least 1 cycle of MATRix chemotherapy in a real-world non-trial setting between 2010 and 2017 at 9 European centers. One cycle consisted of: 2 x rituximab 375 mg/m² before and/or after chemotherapy, MTX 3.5 mg/m² on day 1, AraC 2 g/m² twice daily on days 2 and 3, and thiotepa 30 mg/m² on day 4. Patients were enrolled at the discretion of the treating physician. Main endpoints were theoretical eligibility for the IELSG32 trial, rate of (serious) adverse events, feasibility, remission status after MATRix therapy, progression free survival (PFS) and overall survival (OS).

**Results**

88 patients were included, with a median age of 61 years (range 28–76). Twenty-three patients (26%) would not have met the inclusion criteria of the IELSG32 trial (age > 70 years: 10; reduced performance status [PS]: 4; HIV infection: 3; active hepatitis: 3; inadequate organ function: 3). Anticipated treatment courses were delivered in 228/352 (65%) cases. Dose modifications were performed in 35/88 patients (40%) during cycle 1, in 43/79 patients (54%) during cycle 2, in 33/70 patients (47%) during cycle 3, and in 29/57 patients (51%) during cycle 4. The most common reasons for chemotherapy modification during cycle 1 were reduced PS, co-existing comorbidities and age. Main reasons for dose reduction during subsequent chemotherapy cycles were hematological toxicities, infectious complications and reduced performance. Adverse events, mainly infections, were reported in 48/88 patients (55%) during cycle 1, in 39/79 patients (49%) during cycle 2, in 33/70 patients (47%) during cycle 3, and in 22/57 patients (39%) during cycle 4. Severe infectious complications were more common during cycle 1 (16%) compared to cycle 4 (5%). Intensive care support was required in 4/88 patients (4.5%) during cycle 1, in 1/79 patients (1%) during cycle 2, in 1/70 patients (1.5%) during cycle 3, and in no patients during cycle 4. We recorded six (7%) treatment related deaths during induction chemotherapy (4 during cycle 1, 2 during cycle 2; median patient age 65 years; range 54–75), 5 due to infectious complications and one due to sudden death. Two other patients died later (over 1 year after initiation of MATRix treatment thus not considered treatment related) whilst off therapy and without evidence of disease (one due to hepatic failure and another due to septic encephalitis). After a median of 4 MATRix cycles (range 1–4), the overall response rate was 83% (41% complete remission, 42% partial remission). Nine patients (11%) had progressive disease. Consolidation therapy was applied in 44/82 patients (54%) after MATRix induction therapy (HDT–ASCT: 35; WBRT: 8; lenalidomide: 1). After a median follow-up of 13.1 months, 2-year OS and PFS was 64% (95% CI 52% to 80%) and 57% (95% CI 45% to 72%).

**Conclusions**
The MATRix protocol is feasible and effective in the treatment of newly diagnosed PCNSL in routine practice, and can be delivered to patients aged >70, with reduced PS and/or co-morbidity to produce similar clinical outcomes to the IELSG32 trial. Importantly, close monitoring and consideration of dose reductions is strongly recommended, especially during cycle 1, to avoid treatment associated complications. Further details will be presented at the meeting.

Disclosures Schorb: Riemser: Honoraria. Fox: Janssen: Consultancy, Honoraria, Other: Travel Sponsorship, Speakers Bureau; Roche: Consultancy, Honoraria, Other: Travel Sponsorship, Research Funding, Speakers Bureau; AbbVie: Consultancy, Honoraria, Other: Travel Sponsorship, Research Funding. Yallop: Jazz Pharmaceuticals: Honoraria; Pfizer: Other: Advisory board; Amgen: Honoraria. Cummin: Janssen: Other: Travel reimbursement. Illerhaus: Riemser: Honoraria. Cwynarski: Gilead, Roche: Other: Advisory board; Gilead, Janssen: Other: Conference expenses.

• Asterisk with author names denotes non-ASH members.
• This icon denotes a clinically relevant abstract
© 2017 by The American Society of Hematology

Potential Articles of Interest

The role of whole brain radiation in primary CNS lymphoma
Benjamin Kasenda et al., Blood

Effects on Survival and Neurocognitive Functions of Whole-Brain Radiotherapy (WBRT) and Autologous Stem Cell Transplantation (ASCT) as Consolidation Options after High-Dose Methotrexate-Based Chemoimmunotherapy in Patients with Newly Diagnosed Primary CNS Lymphoma (PCNSL): Results of the Second Randomization of the IELSG32 Trial
Andrés J.M. Ferreri et al., Blood

High-Dose Chemotherapy and Autologous Stem-Cell Transplantation for Primary CNS Lymphoma: Updated Results from a Pilot and Phase II Study
Gerald Illerhaus et al., Blood

Effect of Rituximab in Primary Central Nervous System Lymphoma - results of the Randomized Phase III HOVON 105/ALLG NHL 24 Study
Josée Zijlstra et al., Blood

Population Based Analysis of Outcomes of Primary Central Nervous System Lymphoma (PCNSL) Suggests a Treatment Strategy Including Intensive Chemotherapy with Autologous Stem Cell Transplantation Provides a Survival Advantage for Patients <65 Years of Age
Joanna Graczyk et al., Blood

Novel Treatment Regimen for Newly Diagnosed Primary CNS Lymphoma
PracticeUpdate

Whole-Brain Radiotherapy Does Not Improve Survival in Primary CNS Lymphoma
PracticeUpdate

May 31 - ASCO: Risks of adjuvant WBRT outweigh benefits for patients with limited metastases
News Release, Applied Radiation Oncology

SRS versus WBRT for resected brain metastases – Authors' reply
David Roberge et al., The Lancet Oncology

Brain metastases from HER2-positive breast cancer
Sridhar Papaiah Susheela et al., The Lancet Oncology
Induction Chemo-Immunotherapy with the Matrix Regimen in Patients with Newly Di...