

S219

MATRIX FOLLOWED BY AUTOLOGOUS TRANSPLANT IS ASSOCIATED WITH EXCELLENT SURVIVAL AND NEUROTOLERABILITY IN PRIMARY CNS LYMPHOMA: RESULTS OF THE IELSG32 TRIAL AT A MEDIAN FOLLOW-UP OF 88 MONTHS

Topic: 19. Aggressive Non-Hodgkin lymphoma - Clinical

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Gerald Illerhaus¹, Kate Cwynarski², Elisa Pulczynski³, Christopher Fox⁴, Elisabeth Schorb⁵, Claudia Celico⁶, Monica Falautano⁷, Alessandro Nonis⁸, Paul La Rosée⁹, Mascha Binder¹⁰, Alberto Fabbri¹¹, Fiorella Ilariucci¹², Mauro Krampera¹³, Alexander Röth¹⁴, Claire Hemmaway¹⁵, Peter W M Johnson¹⁶, Kim Linton¹⁷, Tobias Pukrop¹⁸, Jette Sønderskov Gørløv¹⁹, Monica Balzarotti²⁰, Georg Hess²¹, Ulrich Keller²², Stephan Stilgenbauer²³, Jens Panse²⁴, Alessandra Tucci²⁵, Lorella Orsucci²⁶, Francesco Pisani²⁷, Manuela Zanni²⁸, Stefan Krause²⁹, Hans Joachim Schmoll³⁰, Bernd Hertenstein³¹, Mathias Rummel³², Jeffery Smith³³, Lorenz Thurner³⁴, Maria Giuseppina Cabras³⁵, Elsa Pennese³⁶, Maurilio Ponzoni³⁷, Martina Deckert³⁸, Letterio Politi³⁹, Jürgen Finke⁴⁰, Antonella Ferranti⁴¹, Kelly Cozens⁴², Elvira Burger⁴³, Nicoletta Ielmini⁴⁴, Franco Cavalli⁴⁴, Emanuele Zucca⁴⁴, Andrés J.M. Ferrer⁴⁵

¹ Klinikum der Landeshauptstadt Stuttgart gKAÖR

² Department of Haematology UCLH, Informazioni di sicurezza sul COVID-19 University College London Hospitals NHS Foundation Trust, London, United Kingdom

³ Department of Haematology, Aarhus University Hospital, Aarhus, Denmark

⁴ Clinical Haematology City Campus, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom

⁵ Klinik für Innere Medizin I, Universitätsklinikum Freiburg, Freiburg, Germany

⁶ Unità di Neuroriabilitazione, IRCCS San Raffaele Scientific Institute, Milan, Italy

⁷ Institute of Experimental Neurology, IRCCS San Raffaele Scientific Institute, Milan, Italy

⁸ University Centre for Statistics in the Biomedical Sciences, IRCCS San Raffaele Scientific Institute, Milan, Italy

⁹ Klinik für Innere Medizin II, Schwarzwald-Baar Klinikum, VILLINGEN-SCHWENNINGEN, Germany

¹⁰ Zentrum für Onkologie, Universitätskrankenhaus Hamburg-Eppendorf - UKE, Hamburg, Germany

¹¹ UOC Ematologia e trapianti, Azienda ospedaliera universitaria senese, Siena, Italy

¹² Arcispedale Santa Maria Nuova, Azienda Ospedaliera di Reggio Emilia, Reggio Emilia, Italy

¹³ Divisione di ematologia, Policlinico G.B. Rossi, Verona, Italy

¹⁴ Klinik für Hämatologie und Stammzelltransplantation, Universitätsmedizin Essen (AÖR), Essen, Germany

¹⁵ Queen's Hospital, Romford, United Kingdom

¹⁶ UK NCRI Lymphoma Group, Southampton General Hospital, Southampton, United Kingdom

¹⁷ Manchester Cancer Research Centre, University of Manchester, Manchester, United Kingdom

¹⁸ Universitätsklinikum Regensburg, Regensburg, Germany

¹⁹ Department of Hematology, Rigshospitalet, Copenhagen, Denmark

²⁰ Hematology, Humanitas Research Hospital, Rozzano, Italy

²¹ III. Medizinische Klinik und Poliklinik, Universitätsmedizin Mainz, Mainz, Germany

²² III. Medizinischen Klinik des Klinikums rechts der Isar, Technische Universität München, München, Germany

²³ Klinik für Innere Medizin, Universitätsklinikum Ulm, Ulm, Germany

²⁴ Klinik für Innere Medizin IV, Universitätsklinikum Aachen, Aachen, Germany

²⁵ USD Sezione Ematologia, Spedali Civili, Brescia, Italy

²⁶ Ematologia, AOU Città della Salute e della Scienza di Torino, Torino, Italy

²⁷ S.C. Ematologia, Istituto Regina Elena, Roma, Italy

²⁸ SC Ematologia, AO Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

²⁹ Medizinische Klinik 5, Universitätsklinikum Erlangen, Erlangen, Germany

³⁰ Klinik für Hämatologie/Onkologie, Martin-Luther Universität, Halle, Germany

³¹ Medizinische Klinik I, Klinikum Bremen-Mitte GmbH, Bremen, Germany

³² Medizinische Klinik IV, Klinikum der Justus-Liebig-Universität, Giessen, Germany

- ³³ Haematology, University Hospital Aintree, Liverpool, United Kingdom
- ³⁴ Innere Medizin I, Universitätsklinikum des Saarlandes, Homburg, Germany
- ³⁵ Unità Operativa di Ematologia, Ospedale A. Businco, Cagliari, Italy
- ³⁶ Centro diagnosi e terapia dei linfomi, Presidio Ospedaliero Spirito Santo, Pescara, Italy
- ³⁷ Haematopathology Diagnostic Area, IRCCS San Raffaele Scientific Institute, Milano, Italy
- ³⁸ Department of Neuropathology, University of Cologne, Cologne, Germany
- ³⁹ Neuroradiology research, IRCCS San Raffaele Scientific Institute, Milano, Italy
- ⁴⁰ Klinik für Innere Medizin I, Universitätsklinikum Freiburg, Freiburg, Germany
- ⁴¹ Fondazione Italiana Linfomi, Alessandria, Italy
- ⁴² Clinical Trials Unit, University of Southampton, Southampton, United Kingdom
- ⁴³ Projektkoordination Klinische Studien, Universitätsklinikum Freiburg, Freiburg, Germany
- ⁴⁴ International Extranodal Lymphoma Study Group, Foundation for the Institute of Oncology Research, Bellinzona, Switzerland
- ⁴⁵ Unità Operativa di Oncologia Medica, IRCCS San Raffaele Scientific Institute, Milano, Italy

Background: The IELSG32 trial has shown the significantly better activity and acceptable safety profile of MATRIX regimen and a similar efficacy of consolidation with whole-brain irradiation (WBRT) or autologous transplantation (ASCT) in pts ≤ 70 yo with primary CNS lymphoma (PCNSL). However, events after a more extended follow-up remain to be addressed.

Aims: To establish the associations among different treatment arms of the IELSG32 trial and OS, late toxicity, incidence of secondary tumors, and cognitive impairment at a median follow-up of 88 (IQR 77-99) months.

Methods:

HIV-neg pts 18-70 yo with ECOG PS ≤ 3 (PS ≤ 2 if 66-70 yo) with untreated PCNSL were randomly assigned to receive 4 courses of methotrexate-cytarabine (arm A), or arm A plus rituximab (arm B), or arm B plus thiopeta (arm C; MATRIX). Pts with responsive/stable disease were further randomized between WBRT (arm D) and BCNU-thiopeta/ASCT (arm E). Primary endpoints were CRR (1st random) and PFS (2nd random). Effects of treatment on cognitive functions and quality of life (QoL) were addressed comparing results of the IPCG tests panel and EORTC-QLQ performed immediately after treatment and at the last follow-up visit.

Results:

219 assessable pts (median age 58; range 18-70) were randomized (arm A 75; B 69; C 75). After induction, 167 (76%) pts had responsive or stable disease; 118 (71%) of them were further randomized (arm D 59; E 59), whereas 49 pts were excluded (poor mobilizers, poor conditions, patients' refusal).

15 (7%) pts died of toxicity during treatment. 87 (40%) pts remain relapse-free (A 17; B 28; C 42); 14 of them died of infections (n=4), sudden death (4), cognitive decline (3), second tumor (2), and car accident (1). 117 (53%) pts experienced relapse: 96 died of lymphoma, 14 achieved tumor remission upon salvage therapy and remained relapse-free at 39-121 months, while 7 died of complications during salvage therapy. Second cancers were diagnosed in 8 (4%) pts after 48-96 months from WBRT (5) or ASCT (3); two of them were lethal, the other six remained relapse-free after surgical resection. Deaths in relapse-free pts, deaths occurred during salvage treatment and secondary tumors were not significantly related to induction or consolidation treatments (Table).

Neuropsychological tests showed a statistically significant impairment in some attentive and executive functions in pts treated with WBRT, while a significant improvement was noted in these functions as well as in memory and QoL in transplanted pts.

Pts treated with MATRIX (arm C) showed a significantly better PFS, with a 7-yr PFS of $20 \pm 5\%$ for arm A, $29 \pm 6\%$ for arm B and $52 \pm 6\%$ for arm C (A vs C $p=0.00002$; B vs C $p=0.01$). PFS was similar in both consolidation arms (7-yr: $55 \pm 7\%$ and $50 \pm 7\%$; $p=0.35$). 87 pts are alive (arm A 18; B 27; C 42), with a 7-yr OS of $26 \pm 5\%$, $37 \pm 6\%$ and $56 \pm 6\%$, respectively (A vs C $p=0.00007$; B vs C $p=0.03$). OS was similar in both consolidation arms (7-yr: $63 \pm 6\%$ and $57 \pm 6\%$, $p=0.17$). Pts treated with MATRIX and consolidation had a 7-yr OS of $70 \pm 6\%$, without a difference between WBRT and ASCT. In multivariable analysis, IELSG score, number of lesions and induction arm were associated with OS; gender, CSF cytology and consolidation were not.

Image:

Table. Second tumors and late complications in pts who completed the planned treatment

	Arm A (42)	Arm B (50)	Arm C (63)	WBRT (70)*	ASCT (60)*
Second tumors (n=8) [§]	1 (2%)	2 (4%)	5 (8%)	5 (7%)	3 (5%)
Deaths in relapse-free patients (n= 14)	2 (5%)	6 (12%)	6 (9%)	9 (13%)	3 (5%)
Deaths during salvage treatment (n=7)	4 (9%)	0 (0%)	3 (5%)	2 (3%)	2 (3%)

*Actually delivered consolidation within and outside 2nd randomization.

[§]Acute erythroid leukemia, high-grade glioma, melanoma (2), Paget's disease of the breast, prostate cancer, colon cancer, basal cell carcinoma.

Summary/Conclusion:

MATRIX regimen was associated with excellent long-lasting survival in PCNSL pts ≤ 70 ys. WBRT and ASCT exhibit similar efficacy. In comparison with the other therapeutic arms, MATRIX and ASCT were not associated with higher non-relapse mortality and incidence of second tumors, whereas impairment of specific cognitive functions after WBRT was confirmed.

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