No evidence of beneficial effect of plasmapheresis (PLEX) in natalizumab associated PML: pooled analysis of Italian and published international cases

D. Landi[1], N. De Rossi[2], S. Zagaglia[3], C. Scarpazza[2], L. Prosperini[4], M. Albanese[1], F. Buttari[1], F. Mori[1], G. Marfia[1], M. Sormani[5], R. Capra[2], D. Centonze[6] on behalf of the Italian PML group

[1] Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine, Tor Vergata University, 00133 Rome, Italy; [2] Regional Multiple Sclerosis Center, ASST - Spedali Civili di Brescia, 25018, Montichiari, Brescia, Italy; [3] Neurological Clinic, Marche Polytechnic University, 60100 Ancona, Italy; [5]Department of Neurology and Psychiatry, Sapienza University, Rome, Italy, [5] Biostatistics Unit, Department of Health Sciences (DISSAL), University of Genoa, 16132, Genova, Italy, [6]IRCCS Istituto Neurologico Mediterraneo (INM) Neuromed, 86077 Pozzilli (Is), Italy

Background

To date, no treatments for natalizumab related progressive multifocal leukoencephalopathy (PML) exist. In order to limit the infection spreding in the brain, the use of plasma exchange (PLEX) is highly recommended. Although effective in removing NTZ, PLEX might be detrimental for patient outcome. Indeed, PLEX may increase the likelihood of the development of immune reconstitution inflammatory syndrome (IRIS) from the rapid restoration of immunosurveillance, which will eventually worsen the clinical symptoms and the possibility of inflammatory brain damage. Despite this concerns, the effectiveness of PLEX has never been sistematically investigated.

Objective

To retrospectively compare the clinical outcome and survival of Italian and international cases of natalizumab-associated Progressive Multifocal Leukoencephalopathy (NTZ-PML) treated or not with (PLEX).

Table 1. Descriptive characteristics of the population

	PLEX+ n = 184	PLEX– n = 35	p
Sex, n (%)			**0.02**
-Male	61 (33)	4 (11)	
-Female	123 (67)	31 (89)	
Age at PML diagnosis (years), mean (±SD)[a]	43.3 (±8.9)	40.9 (±10.7)	0.26
Country, n (%)			0.36
-Europe	136 (74)	29 (83)	
-US and ROW	48 (26)	6 (17)	
Pre-PML EDSS, median [range][b]	3.5 [0–7.5]	3.5 [1.0–7.0]	0.64
No. of NTZ infusions, mean (±SD)[c]	31.9 (±12.7)	35.9 (±14.8)	0.10
Prior immunosuppressants, n (%)			0.09
-yes	38 (36)	5 (17)	
-no	68 (64)	24 (83)	
EDSS at PML diagnosis, median [range][d]	5.0 [0–9.0]	4.0 [2.0–8.0]	0.62
Symptoms at PML diagnosis, n (%)			0.60
-yes	95 (92)	27 (87)	
-no	8 (8)	4 (13)	
PML lesion localization at diagnosis, n (%)			**0.04**
-supratentorial	69 (87)	17 (68)	
-infratentorial	6 (7)	2 (8)	
-both	5 (6)	6 (24)	
CSF-JCV status at diagnosis, n (%)			0.25
-positive	160 (88)	27 (79%)	
-negative	21 (12)	7 (21%)	
CSF-JCV copies/mL (anytime), median [interval][e]	340 [0–4,831,575]	57 [0–26,300]	**0.001**
Additional treatments, n (%)			**0.002**
-none	35 (38)	23 (72)	
-mefloquine and/or mirtazapine	56 (62)	9 (18)	
PML-IRIS development, n (%)			0.99
-yes	92 (81)	24 (83)	
-no	21 (19)	5 (17)	
PML diagnosis-IRIS interval (days), median [interval][f]	27.5 [0–90]	45 [6–120]	0.14
Treatment with steroids, n (%)			0.99
-yes	72 (80)	26 (81)	
-no	18 (20)	6 (19)	
EDSS at last available follow-up, median [interval][g]	7.5 [0–10]	6.0 [1.5–10]	0.16
Final outcome, n (%)	93	25	0.48
-Improved	19 (21)	7 (28)	
-Stable	15 (16)	4 (16)	
-Worsened	30 (32)	10 (40)	
-Death	29 (31)	4 (16)	
Death, n (%)			0.66
-yes	29 (16)	4 (11)	
-no	152 (84)	31 (89)	
Follow-up time (months), median [interval][h]	11 [<1–35]	12 [<1–26]	0.20

The percentages were estimated from the number of available observations
The number of available observations for PLEX+/PLEX–: [a]182/35, [b]54/20, [c]183/34, [d]40/16, [e]168/30, [f]52/6, [g]66/20, [h]72/25. Abbreviations: PLEX, plasmapheresis; PML, progressive multifocal leukoencephalopathy; SD, standard deviation; US, United States; ROW, rest of world; EDSS, Expanded Disability Status Scale; NTZ, natalizumab; CSF-JCV, cerebrospinal fluid-JC virus; IRIS, immune reconstitution inflammatory syndrome

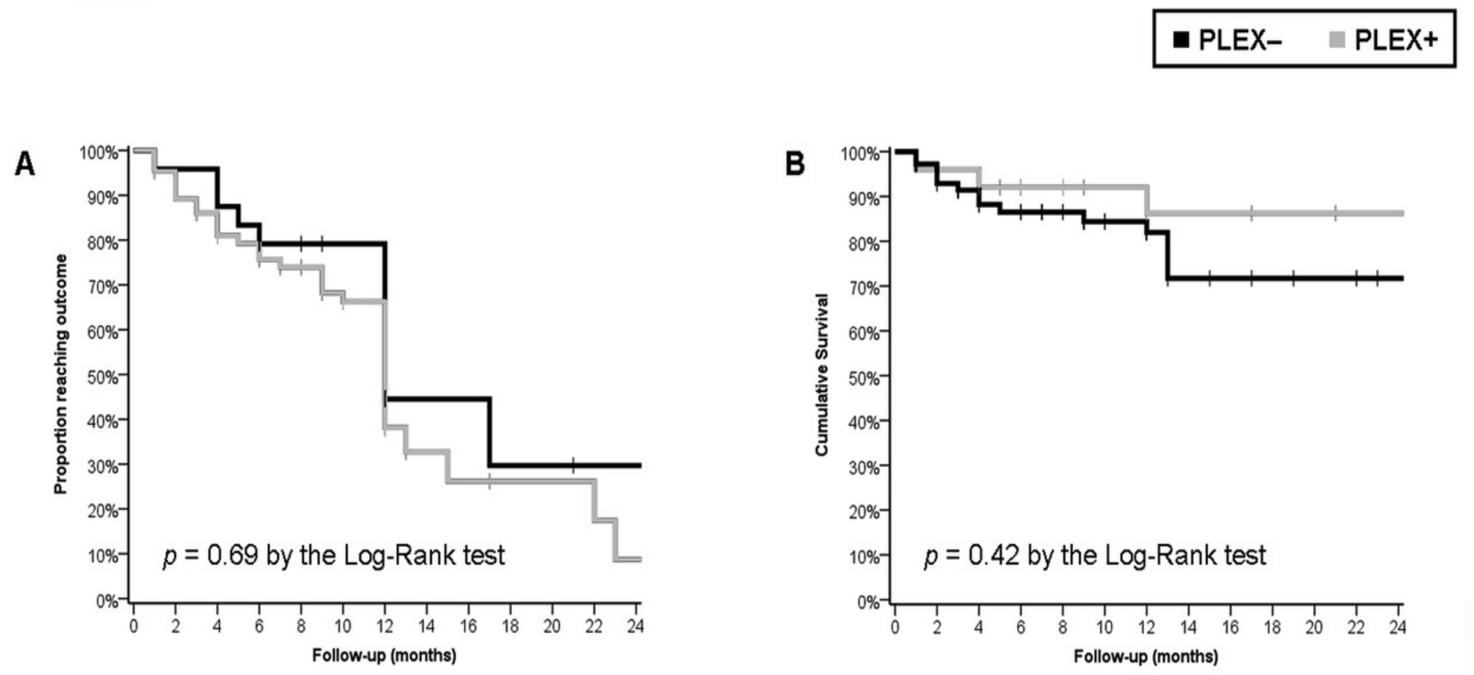
Methods

Medical literature was searched for the terms “Natalizumab” and “Progressive Multifocal Leukoencephalopathy”. Data on 193 NTZ-PML cases, extracted from 49 papers out of 487, aggregate to data derived from 34 Italian cases, were analyzed. Clinical outcome (improved, stable, worsened, dead) was defined comparing clinical status at PML diagnosis and after PML resolution. Death from any cause after PML diagnosis was considered an event in survival analysis. The effect on clinical outcome and survival of PLEX, age, country, lesions location at diagnosis, CSF-JCV status, PML-IRIS was analyzed both by univariate and multivariate analyses using logistic regression models.

Results

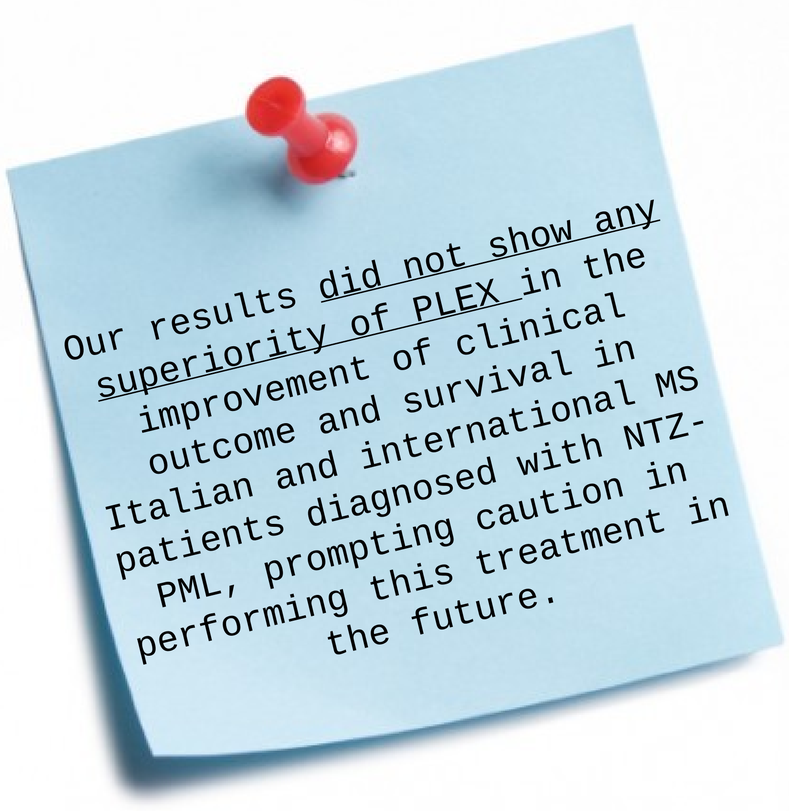
PLEX did not reduce the mortality risk [Hazard Ratio (HR), 1.25; confidence interval (CI), 0.40–3.92; p = 0.7] or the likelihood of bad versus favorable outcomes (HR, 1.25; CI, 0.68–2.32; p = 0.47). At multivariate analysis country (US and ROW) was predictive of mortality (HR, 5.78; CI, 0.97–34.36; p = 0.05) and bad outcome (HR, 3.87; CI, 1.78–8.42; p = 0.001), while PML-IRIS development (HR, 4.61; CI, 1.10–19.39; p = 0.04) was predictive of bad outcome.

Fig.1. Kaplan-Meier curves showing time to outcome (worsening or death, A) and overall survival (B) after PML diagnosis.



Discussion

These findings suggested that the spontaneous recovery of immunocompetence after NTZ withdrawal might counteract the spread of PML in patients with MS and therefore not require any additional intervention. Nevertheless, forcing the rapid restoration of immune surveillance in the brain with PLEX may eventually expose patients to an increased risk of aggressive PML-IRIS. Considering the potential risks and costs of PLEX, we believe that these results argue for caution and for individualized decision-making regarding PLEX. The clinical relevance of this problem justifies the performance of prospective clinical studies in order to identify the patients who will more likely benefit from PLEX in NTZ-PML treatment.



List of collaborators from the Italian PML study group (in alphabetical order): Maria Pia Amato, Fabio Bandini, Antonio Bertolotto, Vincenzo Brescia-Morra, Guido Cavaletti, Paola Cavalla, Marco Capobianco, Marinella Clerico, Giangaetano D’Aleo, Marilena de Riz, Luciano Deotto, Luca Durelli, Mario Falcini, Ernesta Ferrari, Maria Luisa Fusco, Claudio Gasperini, Simonetta Gerevini, Angelo Ghezzi, Luigi Grimaldi, Mario Guidotti, Alessandra Lugaresi, Paola Naldi, Lucia Moiola, Patrizia Perrone, Matteo Pizzorno, Carlo Pozzilli, Monica Rezzonico, Marco Rovaris, Giuseppe Salemi, Marco Salvetti, Giuseppe Santuccio, Elio Scarpini, Edoardo Sessa; Claudio Solaro, Giulia Tabiadon, Carla Tortorella, and Maria Trojano