Addition of Rituximab to the Treatment of Newly Diagnosed Primary CNS Lymphoma is Associated with Improved Outcome: A French LOC Network study

Authors

Caroline Houillier[1], Carole Soussain[2], Hervé Ghesquières[3], Olivier Chinot[4], Luc Taillandier[5], Pierre Soubeyran[6], Franck Morshhauser[7], Alexandra Benouaich-Amiel[8], Guido Ahle[9], Marie-Pierre Moles[10], Roch Houot[11], Cécile Moluçon-Chabrot[12], Pascal Bourquard[13], Gandhi Damaj[14], Fabrice Jardin[15], Vincent Delwail[16], Rémy Gressin[17], Arnaud Jaccard[18], Oumedaly Reman[19], Annie Brion[20], Olivier Casasnovas[21], Philippe Colin[22], Sylvain Choquet[23], Khê Hoang-Xuan[1], and Emmanuel Gyan[24].

Institutions

1. Service de neuro-oncologie, Hôpital Pitié-Salpetrière, Paris, France,
2. Service d'hématologie, Institut Curie, Saint-Cloud, France
3. Service d'hématologie, Centre Léon Bérard, Lyon France
4. Service d'hématologie, Hôpital La Timone, Marseille, France
5. Service d'hématologie, Centre Hospitalier Universitaire, Nancy, France
6. Service d'hématologie, Institut Bergonié, Bordeaux, France
7. Service des maladies du sang, Centre Hospitalier Universitaire, Lille, France
8. Service de neuro-oncologie, Centre Hospitalier Universitaire, Toulouse, France
9. Service d'hématologie, Centre Hospitalier, Colmar, France
10. Service des maladies du sang, Centre Hospitalier Universitaire, Angers, France
11. Service d'hématologie, CHU de Rennes, Rennes, France
12. Service d'hématologie, CHU de Clermont-Ferrand, Clermont-Ferrand, France
13. Service d'hématologie, Centre Hospitalier Universitaire de Nîmes, Nîmes, France
14. Service d'hématologie, Centre Hospitalier Universitaire d'Amiens, Amiens, France
15. Service d'hématologie, Centre Henri Becquerel, Rouen, France
16. Service d'hématologie, Centre Hospitalier Universitaire de Poitiers, Poitiers, France
17. Service d'hématologie, Centre Hospitalier Universitaire de Grenoble, La Tronche, France
18. Service d'hématologie, Centre Hospitalier Universitaire de Limoges, Limoges, France
19. Service d'hématologie, Centre Hospitalier Universitaire de Caen, Caen, France
20. Service d'hématologie, Centre Hospitalier Universitaire de Besançon, Besançon, France
21. Service d'hématologie, Centre Hospitalier Universitaire de Dijon, Dijon, France
22. Service d'hématologie, Institut du Cancer Courlancy, Reims, France
23. Service d'hématologie, Hôpital Pitié Salpêtrière, Paris, France
24. Service d'hématologie, Centre Hospitalier Universitaire, Tours, France

Background

- Primary CNS Lymphoma (PCNSL) initial treatment is based on HD IV methotrexate-based polychemotherapy combinations such as MPV-A, MBVP, Methotrexate and Cytarabine.
- Rituximab has offered an improvement in the treatment of systemic DLBCL
- The role of rituximab in the treatment of PCNSL is unclear
- The practice of French hematology centers is heterogeneous
- A prospective database of PCNSL was set up since 2011 under the auspices of the National Institute of Cancer (INCa)
- The existence of this database represents an opportunity for a retrospective comparison of the outcome of patients treated with or without rituximab

Methods

- Consecutive patients admitted in the participating centers were included in the registry with the following inclusion criteria : (i) age over 18, (ii) pathologically proven PCNSL at initial diagnosis, (iii) actively treated, (iv) with available clinical data on patient characteristics, and treatment.
- Primary objective: PFS, secondary objective: OS
- Patients were divided in twho groups :
  - Patients treated with rituximab (R+)
  - Patient not treated with rituximab (R-)
- Multivariate analysis with a Cox model was used to compare PFS and OS between the two groups.
- A subgroup analysis was performed in the patients older than 60 years.

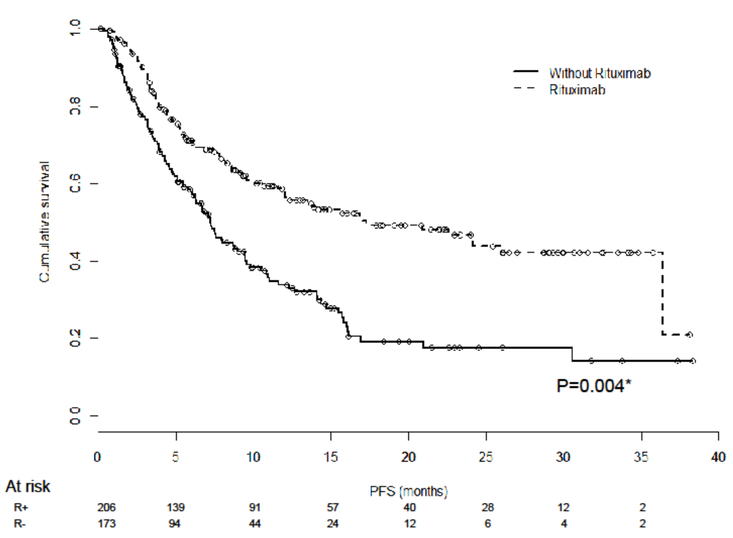
Results

Patient characteristics

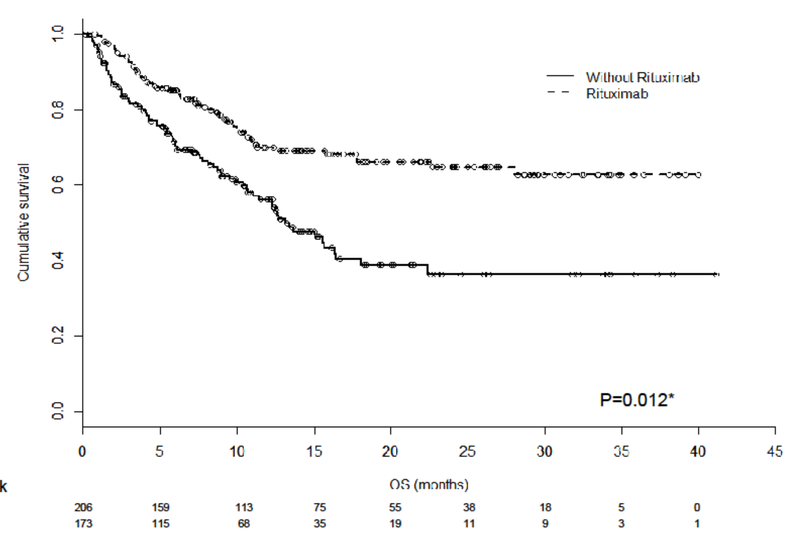
	R- n=173	R+ n=206	All n=379	p
Sex (F) n (%)	94(54)	83(40)	177(47)	0.009
Age, years, median (s.d.)	69.8(8.4)	60.1(11.9)	65.3(11.5)	< 0.001
Karnofsky index (median, [Q1, Q3])	60[50-70]	70[50-80]	60 [50-70]	0.078
Cognitive impairment n (%)				< 0.001
Yes	115(66)	99(48)	214(56)	
No	58(34)	107(52)	165(44)	
Walking disorders				
No	70(40)	86(42)	156(41)	
Yes	97(56)	114(55)	211(56)	
Unknown	6(3)	6(3)	12(3)	
Headache/intracranial hypertension				
No	127(73)	144(70)	271(72)	
Yes	43(25)	61(30)	104(27)	
Unknown	3(2)	1(0)	4(1)	
Seizures				
No	159(92)	183(89)	342(90)	
Yes	12(7)	22(11)	34(9)	
Unknown	2(1)	1(0)	3(1)	
Sensorymotor impairment				
No	107(62)	131(64)	238(63)	
Yes	64(37)	69(33)	133(35)	
Unknown	2(1)	6(3)	8(2)	
Phasic disorders				
No	126(73)	179(87)	305(80)	
Yes	44(25)	26(13)	70(18)	
Unknown	2(1)	0(0)	2(1)	
Balance disorders				
No	120(69)	136(66)	156(41)	
Yes	47(27)	64(31)	111(29)	
Unknown	6(3)	3(1)	9(2)	
Ophtalmic involvement				
Yes	13(8)	18(9)	31(8)	
No	61(35)	95(46)	156(41)	
Unknown	94(54)	90(44)	184(49)	
Imaging pattern				
Unique lesions	97(56)	103(50)	200(53)	
Multiple lesions	58(34)	83(40)	141(37)	
Diffuse involvement	14(8)	14(7)	28(7)	
Other hematologic malignancy				
No	169(98)	203(99)	372(98)	
Yes	2(1)	2(1)	4(1)	
Unknown	2(1)	1(0)	2(1)	
Immunosuppression				
No	166(96)	199(97)	365(96)	
Yes	4(2)	5(2)	9(2)	
Unknown	2(1)	1(0)	3(1)	
Consolidation n (%)	10(6)	76(37)	86(23)	< 0.001
Intrathecal treatment				
Yes	23(13)	49(24)	72(19)	
No	131(76)	143(69)	274(72)	
Protocol n (%)				< 0.001
AraC*	0(0)	3(1)	3(1)	
MPV-A	119(69)	56(27)	175(46)	
MTX-AraC	27(16)	111(54)	138(36)	
MTX-based	27(16)	36(17)	63(17)	

* : the 3 patients treated with HD-AraC were grouped with the patients treated with HDMTX + AraC. MPV-A: HDMTX + vincristine + procarbazine followed by HD-AraC consolidation. MTX-AraC : HDMTX + AraC combinations. MTX-based: HDMTX without HD-AraC.

Progression-free survival



Overall survival



*: the treatment groups are unbalanced for PCNSL prognostic factors

Multivariable analysis

	PFS			OS		
Variable	HR	95%CI	p	HR	95%CI	p
Rituximab (yes vs. no)	0.74	[0.55; 0.99]	0.045	0.77	[0.54; 1.10]	0.155
Sex (M vs. F)	1.40	[1.06; 1.85]	0.019	1.36	[0.96; 1.93]	0.082
Age (per 1-year increment)	1.01	[0.99; 1.02]	0.738	1.03	[1.01; 1.05]	0.007
Karnofsky Index (per 10-increment)	0.94	[0.87; 1.02]	0.080	0.88	[0.80; 0.98]	0.015
Cognitive impairment (yes vs. no)	1.30	[0.93; 1.81]	0.123	1.44	[0.95; 2.18]	0.088
Consolidation (yes vs. no)	0.20	[0.11; 0.33]	<0.001	0.18	[0.09; 0.39]	<0.001
Protocol			0.053			0.004
MPV-A	1.00	-		1.00	-	
MTX-ARAC	1.38	[0.96; 1.98]		1.59	[1.03; 2.45]	
MTX-based	1.59	[1.07; 2.37]		2.14	[1.36; 3.36]	

Multivariable analysis in patients older than 60 years

	PFS			OS		
Variable	HR	95%CI	p	HR	95%CI	p
Rituximab	0.62	[0.44; 0.87]	0.006	0.61	[0.41; 0.92]	0.018
Sex (M vs. F)	1.41	[1.02; 1.95]	0.036	1.35	[0.92; 1.98]	0.122
Age (per 1-year increment)	1.02	[1.00; 1.05]	0.101	1.04	[1.01; 1.07]	0.016
Karnofsky Index (per 10-increment)	0.91	[0.83; 1.00]	0.069	0.86	[0.77; 0.96]	0.009
Cognitive impairment (yes vs. no)	1.33	[0.89; 1.98]	0.162	1.41	[0.87; 2.27]	0.163
Consolidation (yes vs. no)	0.44	[0.20; 0.99]	0.048	0.46	[0.18; 1.19]	0.110
Protocol			0.146			0.031
MPV-A	1.00	-		1.00	-	
MTX-ARAC	0.96	[0.60; 1.54]		1.11	[0.65; 1.91]	
MTX-based	1.54	[1.00; 2.38]		1.97	[1.22; 3.19]	

Discussion

Rituximab exposure was associated with younger age, higher Karnofsky score, less cognitive impairment, and a higher number of patients receiving post-chemotherapy consolidation by radiation or autologous SCT. However, multivariable analysis taking into account the identified recruitment biases identifies an association between rituximab exposure and an improved outcome. These results are in line with other retrospective evaluations (Birnbaum et al, J Neurooncol 2012, Hodlhoff et al., Neurology 2014).

Conclusions

In this nationwide study on untreated PCNSL, rituximab exposure is associated with a prolonged PFS, and an improved OS in patients older than 60 years. These results warrant further research on the role of rituximab in untreated PCNSL therapy.

Conflict of interest : EG received research support from ROCHE.

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Aggressive B-cell lymphoma

Emmanuel Gyan

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