Case Report

Survival of Secondary Central Nervous System Lymphoma Patients in the Rituximab Era

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Clinical Practice Points

- CNS relapse can occur in 2% to 24% of patients with NHL, depending on the subtype.
- Although it has minimal blood–brain barrier penetration, rituximab has been used in primary CNS lymphoma and secondary CNS lymphoma regimens.
- Although overall and event-free survival have improved with to rituximab, the effect on survival after CNS relapse remains unclear.
- We identified 46 NHL patients diagnosed with CNS relapse from 2005 to 2013 at a single institution in Western New York.
- NHL patients who had received rituximab after their CNS relapse had a 53% decreased risk of death compared with those patients who had not received rituximab after their CNS relapse, controlling for speech disturbance as a symptom of CNS relapse and methotrexate use after CNS relapse (95% confidence interval, 0.23-0.97).
- In the absence of randomized data, we suggest including rituximab in the therapeutic regimens for patients with CNS relapse of NHL.

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Introduction

In a review of 14 studies, the incidence of central nervous system (CNS) relapse ranged from 2.3% to 10% of patients with non-Hodgkin lymphoma (NHL; excluding acute lymphoblastic leukemia/lymphoblastic lymphoma and Burkitt lymphoma), with an overall risk of CNS relapse of 4.7%.[1] Indolent lymphomas such as follicular lymphoma and mantle cell lymphoma do not spread to the brain as frequently as do the high-grade lymphomas such as acute lymphoblastic leukemia/lymphoblastic lymphoma and Burkitt lymphoma (2.8% and 24.4%, respectively).[2]

Rituximab has been incorporated into regimens for primary CNS lymphoma (PCNSL) and secondary CNS lymphoma (SCNSL) with methotrexate and cytarabine, although it has minimal blood–brain barrier (BBB) penetration.[3,4] In a pilot study, the use of rituximab as a single agent also resulted in radiographic responses in one third of patients with PCNSL, suggesting activity of rituximab in CNS tumors.[5] Many SCNSL patients were previously exposed to rituximab for treatment of their systemic disease as a part of the initial regimens. However, in the absence of a CNS tumor and a disrupted BBB, they would not have had significant exposure to rituximab in the CNS. In a study of PCNSL, in which patients received a combination of high-dose methotrexate, high-dose cytarabine, and high-dose rituximab, the mean cerebrospinal fluid level of rituximab was 2.04 μg/mL (range, 0.49-4.08 μg/mL), and the serum level was 297.09 μg/mL (range, 211.26-504.47 μg/mL).[6] Therefore, it is logical to conclude that the rituximab-naive tumor cells in the CNS with a newly disrupted BBB might benefit from incorporating rituximab into a multiagent regimen at CNS relapse to treat SCNSL.

Since the implementation of rituximab, NHL patients have experienced longer event-free and overall survival than those patients who did not receive rituximab.[7,8] However, whether rituximab has improved the outcomes for patients with CNS involvement is not clear. Ferreri et al.[9] suggested the combination of rituximab and high doses of antimetabolites, followed by high-dose sequential chemoimmunotherapy and autologous stem cell transplantation as the current standard therapy for SCNSL, because this therapy was feasible and effective in this patient population. However, the effect of rituximab alone has not yet been analyzed in

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Table 1 Patient Characteristics Stratified by Rituximab Use after CNS Relapse

Characteristic	Rituximab (n = 18)	No Rituximab (n = 28)
Male gender	11 (61.1)	19 (67.9)
White race	17 (94.4)	27 (96.4)
Subtype		
DLBCL	11 (61.1)	21 (75.0)
Transformed	2 (11.1)	3 (10.7)
MZL	2 (11.1)	1 (3.6)
Burkitt lymphoma	2 (11.1)	1 (3.6)
Lymphoplasmacytic	0 (0)	1 (3.6)
MCL	1 (5.6)	0 (0)
PTLD-DLBCL	0 (0)	1 (3.6)
Age at initial diagnosis (years)		
Median	64.3	62.4
Range	19.6-82.2	25.6-94.1
Age at CNS relapse (years)		
Median	66.5	63.2
Range	19.6-84.6	26.6-94.8
Stage at initial diagnosis		
I	1 (5.6)	3 (13.0)
II	0 (0)	3 (13.0)
III	0 (0)	4 (17.0)
IV	17 (94.4)	14 (58.0)
Missing	0	4
B symptoms at diagnosis		
Yes	5 (35.7)	9 (64.0)
No	9 (64.3)	5 (36.0)
Missing	4	14
Other sites of metastasis before SCNSL	17 (94.4)	21 (80.8)
Bone marrow	4 (23.5)	8 (38.1)
Bone	7 (41.2)	4 (19.0)
Lung	3 (17.6)	4 (19.0)
Liver	2 (11.8)	4 (19.0)
Spleen	2 (11.8)	2 (9.5)
Skin	1 (5.9)	1 (4.8)
Adrenal gland	0 (0)	1 (4.8)
Other	13 (76.5)	9 (42.9)
Missing	1	2
LDH at diagnosis (IU/L)		
Median	273	333
Q1-Q3	202-654	283-890
CNS prophylaxis	1 (6.3)	4 (14.3)
Missing documentation	2	0
Treatment after CNS relapse		
CHOP	10 (55.6)	0 (0)
Rituximab	18 (100)	0 (0)
Methotrexate	13 (72.2)	17 (60.7)
ICE	1 (5.6)	1 (3.6)
Autologous stem cell transplantation	2 (11.1)	1 (3.6)
Allogeneic stem cell transplantation	0 (0)	1 (3.6)
Radiation	5 (27.8)	7 (25.0)
Ara-C/cytarabine	10 (55.6)	7 (25.0)

Table 1 Continued

Data presented as n (%).
Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine (Oncovin), prednisone; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; ICE = ifosfamide, carboplatin, etoposide; LDH = lactate dehydrogenase; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; PTLD = post-transplant lymphoproliferative disease; Q = quartile; SCNSL = secondary central nervous system lymphoma.

Table 2 Subject CNS Characteristics Stratified by Rituximab Use After CNS Relapse

Characteristic	Rituximab (n = 18)	No Rituximab (n = 28)
Site of CNS disease		
Leptomeningeal disease	11 (61.1)	10 (35.7)
Parenchymal tissue	6 (33.3)	13 (46.4)
Both	1 (5.6)	5 (17.9)
Site of parenchymal involvement		
Frontal	3 (42.9)	7 (38.9)
Parietal	3 (42.9)	6 (33.3)
Temporal	2 (28.6)	6 (33.3)
Cerebellum	2 (28.6)	2 (11.1)
Occipital	1 (14.3)	2 (11.1)
Pons	0 (0)	1 (5.6)
Nonspecific	1 (14.3)	1 (5.6)
No. of metastases		
Single	2 (33.3)	7 (46.7)
Multiple	4 (66.7)	8 (53.3)
Missing	1 (14.28)	3 (16.66)
Side		
Right	1 (14.3)	6 (33.3)
Left	3 (42.9)	9 (50)
Both	3 (42.9)	3 (16.7)
Symptoms		
Asymptomatic	4 (22.2)	1 (3.6)
Headache	6 (33.3)	8 (28.6)
Visual changes	5 (27.8)	8 (28.6)
Motor weakness	5 (27.8)	4 (14.3)
Cognitive problems	0 (0)	8 (28.6)
Speech disturbance	3 (16.7)	4 (14.3)
Seizures	1 (5.6)	5 (17.9)
Nausea	3 (16.7)	2 (7.1)
Vomiting	2 (11.1)	2 (7.1)
Other	8 (44.4)	12 (42.9)

Data presented as n (%).
Abbreviation: CNS = central nervous system.