Prognostic impact of immunohistological profiling in primary CNS lymphoma

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Background: Despite improvements in the treatment of primary CNS lymphoma (PCNSL), the response to chemotherapy remains heterogeneous and overall prognosis poor. Thus, identification of predictive and prognostic biomarkers for risk-stratified treatment decisions is highly desirable. We investigated the prognostic significance of B cell differentiation status and common B cell differentiation markers in 119 PCNSL patients homogenously treated with high-dose methotrexate (HDMTX)-based chemotherapy within the G-PCNSL-SG1 trial.

Methods: Protein expression of BCL-2, BCL-6, CD10 and MUM-1/IRF-4 were evaluated by immunohistochemistry, and the association with survival was analyzed.

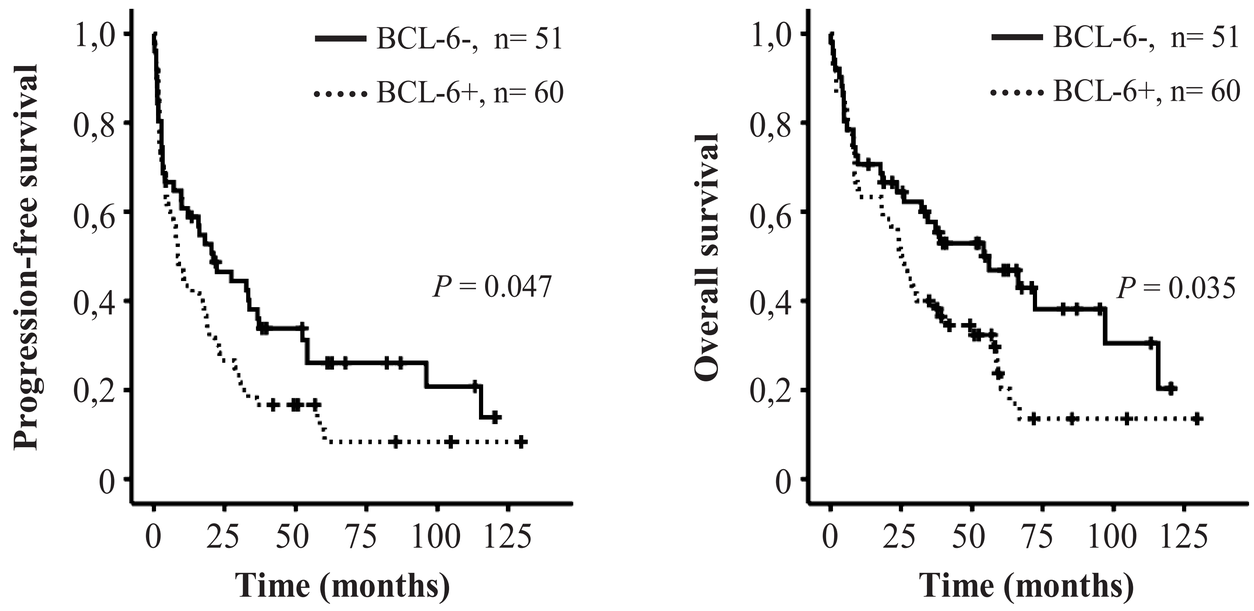
Results: The median follow-up of all patients was 67.5 months. The median progression-free survival (PFS) was 10.61 (95% CI 4.23-17.00) months; the median overall survival (OS) was 28.85 (95% CI 17.96-39.73) months. Eighty-nine tumors expressed BCL-2 (92.7%), 24 (20.5%) CD10, 60 (54.1%) BCL-6 and 87 (79.0%) MUM-1/IRF-4. On the basis of the Hans algorithm, 80 (73.4%) tumors were classified to the non-GCB group suggesting a post germinal center origin of PCNSL. BCL-6 expression (cut-off point 30%), but none of the other markers, was associated with shorter PFS (P=0.047) and OS (P=0.035).

Table 1: Univariate and multivariate analyses for PFS and OS

	Univariate analysis			Multivariate analysis		
	Hazard ratio	P value	95% CI	Hazard ratio	P value	95% CI
PFS						
Age*	1.01	0.32	0.99-1.03	n.d.	---	---
KPS†	0.99	0.23	0.98-1.01	n.d.	---	---
Gender#	0.81	0.29	0.54-1.20	0.69	0.108	0.44-1.08
Multifocal brain involvement◊	1.79	0.011	1.14-2.80	1.20	0.49	0.71-2.03
MSKCC score+	1.40	0.14	0.89-2.20	1.87	0.011	1.15-3.04
LDH○	1.27	0.43	0.70-2.28	1.41	0.32	0.72-2.76
Surgery (biopsy vs. resection)	1.28	0.24	0.85-1.91	0.94	0.80	0.57-1.54
HDMTX versus HDMTX/IFO	0.99	0.97	0.62-1.58	1.00	1.00	0.60-1.67
BCL-2‡‡	1.28	0.60	0.52-3.17	1.09	0.86	0.43-2.77
BCL-6††	1.53	0.047	1.01-2.34	1.95	0.005	1.22-3.12
CD10##	0.81	0.42	0.49-1.34	0.82	0.46	0.47-1.40
MUM-1/IRF-4**	0.96	0.89	0.58-1.60	0.77	0.37	0.43-1.37
GCB/non-GCB++	1.12	0.65	0.70-1.80	1.20	0.49	0.72-2.00
OS						
Age*	1.027	0.026	1.003-1.05	n.d.	---	---
KPS†	0.99	0.044	0.97-1.00	n.d.	---	---
Gender#	0.75	0.20	0.49-1.16	0.48	0.091	0.20-1.13
Multifocal brain involvement◊	1.47	0.11	0.91-2.39	2.72	0.019	1.18-6.28
MSKCC score+	1.66	0.041	1.02-2.70	2.95	0.016	1.22-7.13
LDH○	1.10	0.77	0.59-2.05	1.89	0.38	0.46-7.80
Surgery (biopsy vs. resection)	1.17	0.50	0.75-1.82	0.82	0.67	0.33-2.02
HDMTX versus HDMTX/IFO	0.92	0.76	0.53-1.60	0.37	0.19	0.084-1.63
BCL-2‡‡	0.94	0.89	0.38-2.33	0.68	0.62	0.16-3.01
BCL-6††	1.66	0.035	1.04-2.65	1.85	0.21	0.71-4.80
CD10##	0.61	0.09	0.35-1.07	1.00	1.00	0.39-2.57
MUM-1/IRF-4**	1.00	0.99	0.57-1.77	2.13	0.32	0.48-9.41
GCB/non-GCB++	1.46	0.17	0.86-2.48	1.14	0.79	0.44-2.98

After adjustment for MSKCC score on multivariate analysis BCL-6 expression was associated with shorter PFS (HR 1.95, 95% CI 1.22-3.12, P=0.005) but not OS (HR 1.85, 95% CI 0.71-4.80, P=0.21). Classification according to Hans algorithm and expression status of BCL-2, CD10 and MUM-1/IRF-4 did not correlate with prognosis.

Figure 1: Comparison of progression-free survival and overall survival according to BCL-6 expression.



Conclusion: The prognostic utility of B cell differentiation status and various B cell differentiation markers to predict outcome in PCNSL patients is currently questionable. Our data confirm an activated B cell like immunophenotype and post-GC origin of most PCNSL and indicate BCL-6 expression as a valuable biomarker for inferior prognosis. In view of the fact that several previous studies reported contradicting results, further prospective studies are necessary to validate our results.

Kreher et al., Neuro Oncol. 2015 Mar 26.