Impact on survival of *MYC* genetic alterations but not *MYD88*^{L265P} mutation in primary testicular DLBCL

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INTRODUCTION

- One of the main prognostic markers in nodal or non testicular extranodal diffuse large B-cell lymphoma (DLBCL) is the rearrangement and/or the high protein expression of MYC. The co-expression of MYC and BCL2 is associated with an unfavorable response to R-CHOP. *MYD88* mutation in L265P, which is described in activated B-cell like (ABC) DLBCL, is correlated with a worse prognosis.
- Primary testicular DLBCL is characterized by ABC profile, recurrent *MYD88*^{L265P} mutation, frequent BCL2 expression, but low incidence of *MYC* genetic alterations and protein expression. However, the impact of these features on survival is still unknown.
- The aim of our study was to determine the incidence and the prognostic significance of *MYD88*^{L265P}, MYC and BCL2 gene and protein status in a series of primary testicular DLBCL.

METHODS

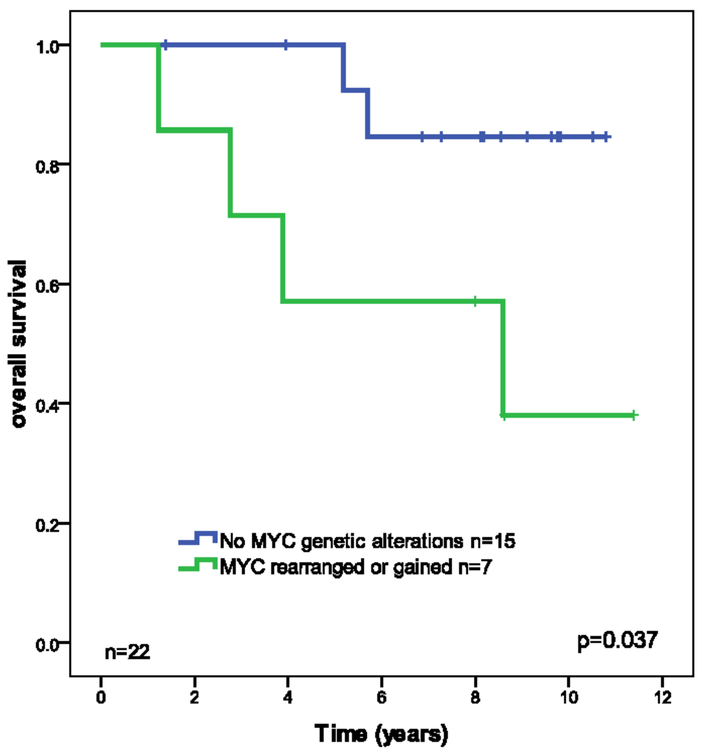
- Our series included 33 primary testicular DLBCL (24 uniformly treated with R-CHOP immunochemotherapy and intrathecal methotrexate in the IELSG-10 clinical trial).
- Immunohistochemical studies were performed using: CD20, CD79a, CD10, BCL6 and MUM1/IRF4, which were evaluated following the Lunenburg Lymphoma Biomarker Consortium. BCL2 was evaluated using a cut-off of 50% and a cut-off of 40% for MYC was used to interpret the results as positive.
- Fluorescence in situ hybridization (FISH) using break apart probes were used to analyze *MYC* and *BCL2* gene status.
- *MYD88*^{L265P} was determined by Sanger Sequencing.
- Chi-square test was used for statistical analysis. Survival was estimated with the Kaplan-Meier method and survival curves were compared using the log-rank test.

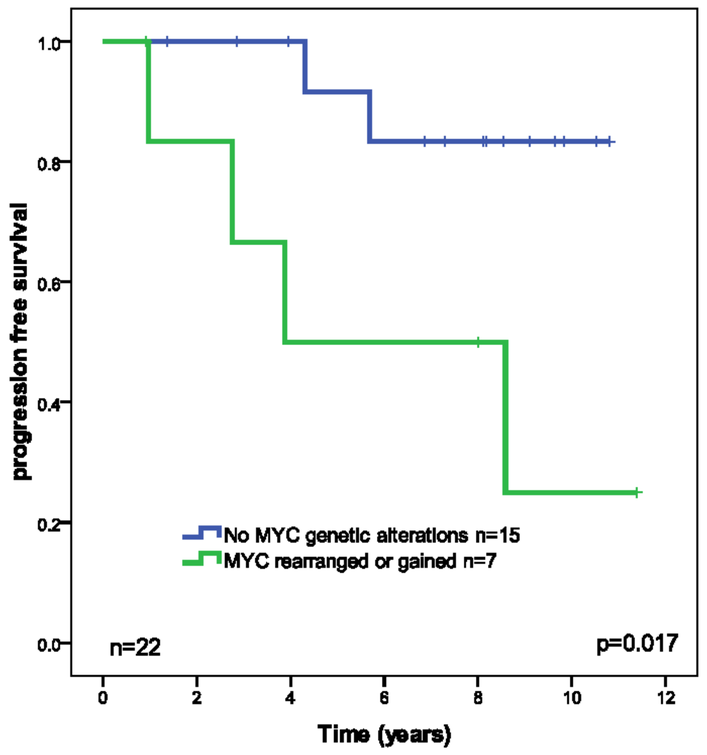
RESULTS

Clinical features		Immunohistochemical features		Genetic features	
Mean age	69 (34-81)	CD10+	4/32 (13%)	*MYC* alterations	10/33 (30%)
> 70 years	17/33 (52%)	BCL6+	22/32 (69%)	▪ *MYC* rearrangement	3/33 (9%)
Ann Arbor Stage IE	16/24 (67%)	MUM1+	26/32 (81%)	▪ *MYC* gains	7/33 (21%)
ECOG zero	22/24 (92%)	Non-GCB	27/32 (84%)	*BCL2* alterations	14/26 (54%)
High LDH	4/22 (18%)	BCL2+	19/30 (63%)	▪ *BCL2* rearrangement	0/26 (0%)
Elevated β2M	2/18 (11%)	MYC+	6/31 (19%)	▪ *BCL2* gains	14/26 (54%)
IPI score 0-1	19/22 (86%)	MYC+BCL2+	6/41 (15%)	*MYD88*^{L265P}	18/33 (55%)

- *MYD88*^{L265P} was observed in 13/17 (76%) patients older than 70 years, whereas 11/16 (69%) patients with 70 or younger were wild type (p=0.009).
- MYC expression was observed in all cases with rearrangement, whereas in 4/6 (67%) with gains and in 19/20 (95%) without alterations, did not show expression of the protein (p=0.001)
- 5/6 (83%) cases with *MYC* gains also showed *BCL2* gains.
- The mean of OS and PFS were 7.28 (1.2-12) and 6.63 (0.9-12) years, respectively, and *MYC* genetic alterations was the only variable predicting an unfavourable outcome (see Figure 1).

Figure 1. The impact on survival of *MYC* genetic alterations in patients treated with the IELSG 10 clinical trial





CONCLUSIONS

- *MYD88*^{L265P} is a common genetic event in DLBCL of the testis and recurrently found in elderly patients.
- *MYC* genetic alterations but not the presence of *MYD88*^{L265P}, neither the expression of MYC (in co-expression or not with BCL2) had an impact on the survival in patients treated with the IELSG-10 clinical trial.
- Other mechanisms apart from rearrangement must be implicated in MYC overexpression in testicular DLBCL, since this expression was also observed in cases without the translocation.
- MYC expression is detected with a low incidence, contrary to CNS DLBCL, suggesting that the role of MYC in their pathogenesis might be different, despite both are immuno-privileged site lymphomas.
- Most of the cases with *MYC* gains also presented gains of *BCL2*, which suggests the presence of complex karyotype that might explain its unfavorable impact on survival.

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