Impact of Metformin Use on the Outcome of Diffuse Large B-Cell Lymphoma

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Background

- The PI3K/mTOR pathway is important for cell proliferation and survival in diffuse large B-cell lymphoma (DLBCL).
- The mTOR inhibitor everolimus has encouraging clinical activity in untreated and relapsed/refractory DLBCL.¹⁻³
- Metformin was shown to have anti-lymphoma activity *in vitro* via mTOR inhibition,⁴ but it's unclear whether it also has clinical activity against lymphoma.
- The objective of this study is to investigate whether metformin use in patients with newly diagnosed DLBCL affected clinical outcomes.

Methods

- 869 patients with newly diagnosed DLBCL from March 2002 to June 2015 at Mayo Clinic were included.
- Patients were enrolled in the Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE) and followed prospectively.
- Patients who were on metformin at the time of DLBCL diagnosis or started metformin within 6 months after DLBCL diagnosis were assigned to the metformin group.
- Event-free survival (EFS) was defined as time from diagnosis to progression or relapse, unplanned re-treatment after initial therapy, or death from any cause. Overall survival (OS) was defined as time from diagnosis to death from any cause.
- Categorical data were analyzed by Chi-square test, and time-to-event data were analyzed using Kaplan-Meier method and Cox regression model.
- Statistical analysis was done in SPSS.

Table 1. Association of metformin use with clinical characteristics

	Metformin	%	No Metformin	%	P value
Age					0.084
≤60	13	27.1	325	39.6	
>60	35	72.9	496	60.4	
Median (range)	69 (43-87)		64 (18-93)		0.017
Gender					0.678
Male	29	60.4	471	57.4	
Female	19	39.6	350	42.6	
ECOG PS					0.443
<2	41	85.4	729	89.0	
≥2	7	14.6	90	11.0	
LDH					0.049
Normal	14	30.4	331	45.3	
Elevated	32	69.6	400	54.7	
Extranodal sites					0.175
≤1	42	87.5	652	79.4	
>1	6	12.5	169	20.6	
Ann Arbor stage					0.186
I-II	16	33.3	353	43.0	
III-IV	32	66.7	457	57.0	
IPI score					0.141
0-1	10	20.8	305	37.1	
2	18	37.5	226	27.5	
3	14	29.2	206	25.1	
4-5	6	12.5	84	10.2	
Cell of origin					0.740
GCB	19	63.3	337	60.3	
Non-GCB	11	36.7	222	39.7	

- 48 (5.5%) patients were in the metformin group.
- Metformin dose ranged from 500 mg daily to 1000 mg twice daily.
- The median duration of metformin use was 37.6 months.

Figure 1. EFS and OS by metformin use status

Table 2. Cox regression analysis of the impact of metformin use on EFS and OS

	HR *	95% CI	P value
EFS (univariate)	1.333	0.881 – 2.016	0.174
EFS (multivariate) #	1.047	0.596 – 1.842	0.872
OS (univariate)	1.376	0.873 – 2.169	0.169
OS (multivariate) #	1.103	0.596 – 2.041	0.755

* Metformin vs No Metformin

Adjusted for IPI and cell of origin.

HR: hazard ratio; 95% CI: 95% confidence interval.

Conclusions

- Metformin use in patients with newly diagnosed DLBCL was associated with an older age.
- Metformin use did not affect EFS or OS in patients with newly diagnosed DLBCL.
- The survival results should be interpreted with caution given the small number of patients in the metformin group.

References

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