Metformin in Combination With the Standard Therapy in Patients With Diffuse Large B-Cell Lymphoma: A Randomized Phase II Clinical Trial

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INTRODUCTION

Metformin has been demonstrated to possess antitumor activity in different tumor types. There is also accumulating evidence that supports an association of metformin use with improved outcome of several types of solid tumors. In this study, we aimed to investigate the efficacy of adding metformin to standard chemotherapy in patients with diffuse -large B -cell lymphoma.

AIM

In this study, evaluated the effect of adding metformin to standard first line therapy (R-CHOP) in diffuse large B cell lymphoma patients.

Primary end point

- Toxicity and Response rate

Secondary end point:

- Disease free survival and Overall survival

METHODS

Group I (trial arm): This arm included 50 patients. Those patients had received metformin together with the standard therapy (R-CHOP) [rituximab 375 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 750 mg/m^2, vincristine 2 mg and prednisolone 100 mg for 5 days). Metformin was administered at a dose of 1000 mg twice daily in uninterrupted 3-weeks cycles. The dose was increased stepwise (500-mg steps) within 2 weeks to the target dose continuously till disease progression, unacceptable drug toxicity or patient withdrawal.

Group II (control arm): This arm included 50 patients; those patients had received the standard therapy (R-CHOP). The same doses for R-CHOP were used as in patients in group I.

RESULTS

We included 100 patients who started treatment between January 2021 and September 2022 (50 assigned to metformin+ (RCHOP) and 50 assigned to (R-CHOP). Patients in the metformin arm had higher rates of complete remission at first restaging (56% vs 32%; *P*=0.016), higher rates of complete remission at end of treatment (94% vs 66%; *P*=0.001), lower rates of relapse/progression (6% vs 54%; *P*<0.001), and lower rates of overall mortality (4% vs 24%; *P*=0.004). There was a higher likelihood of nausea in the metformin arm compared with the control arm (32% vs 14%; p*P*=0.032).

No significant differences were found between metformin and control arms in the risk of other adverse events, including neutropenia, anemia, thrombocytopenia, diarrhea, mucositis, hypoglycemia, vomiting, and metallic taste (all *P*-values > 0.05).

Table (1): Univariate and multivariate analyses of factors affecting development of CR

Parameters	Percent (%)	Univariate				Multivariate
		P-value	Odds ratio (OR)	95%CI		P-value
				Lower limit	Upper limit	
Age						
≤60y	65%	.559	.727	.250	2.115	
>60y	35%					
Stage						
Early	8%	.534	1.711	.315	9.303	
Advanced	92%					
LDH						
High	74%	.725	1.230	.388	3.903	
Normal	26%					
B2M						
High	18%	.468	1.791	.372	8.635	
Normal	82%					
Extra-nodal						
Present	39%	.731	.826	.279	2.452	
Absent	61%					
PS						
≤1	89%	.912	.912	.179	4.654	
>1	11%					
IPI risk group		.				
Low risk	38%	206	.643	.325	1.274	
Low-intermediate	40%					
High-intermediate	17%					
High risk	5%					
Type of pathology						
Activated B cell	21%	.006*	4.786	1.560	14.689	**.013***
Germinal center B cell	79%					

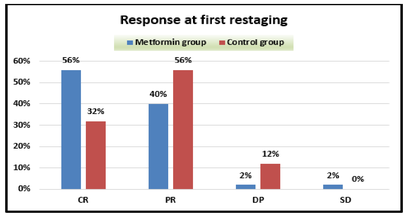


Figure (1): Comparison between study groups regarding response at first restaging.

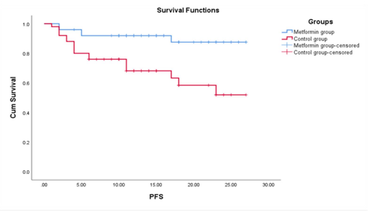


Figure (2): Kaplan-Meier survival curves for progression free survival.

CONCLUSIONS

Adding metformin to standard chemotherapy in patients with diffuse large B -cell lymphoma led to improvement in efficacy without added toxicity. Further studies with large numbers and subgroup analysis for certain types of DLBCL are needed.

REFERENCES

Pokorny, R.; Stenehjem, D.D.; Gilreath, J.A. Impact of metformin on tyrosine kinase inhibitor response in chronic myeloid leukemia. J. Oncol. Pharm. Pract. 2022, 28, 10781552221077254

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