Systemic high-dose methotrexate (HD-MTX) consolidation in poor-risk diffuse large B-cell lymphoma is associated with improved survival in patients with Germinal Centre B-cell phenotype

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Background

Patients with poor-risk Diffuse large B-cell lymphoma (R-IPI>2) have a disappointing response to standard R-CHOP based therapy with 4-year progression free survival (PFS) and overall survival (OS) of 53% and 55% respectively[1]. To date, dose-intense regimens have largely failed to improve these outcomes[2,6].

Since 2007 we have been administering two cycles of systemic high dose methotrexate (HD-MTX) following 6 cycles R-CHOP21 induction, in an effort to reduce the incidence of CNS recurrence in patients at high risk including those with R-IPI ≥3 or involvement of a single high risk site including: renal, adrenal, testicle, female urogenital tract, skin, liver and paravertebral[3,4].

This study examines the impact of systemic HD-MTX on prevention of CNS and extra-CNS systemic relapse compared to a historical cohort of 62 patients who did not receive systemic HD-MTX.

Methods

Eligible patients were identified from the Monash Haematology DLBCL database which includes clinical information on all patients managed at Monash Health. Patients were eligible for inclusion if they had DLBCL diagnosed according to WHO 2008 criteria, completed CHOP-like chemotherapy with Rituximab, and had adequate clinical notes (*n*=405). Of these, 104 patients had R-IPI ≥3 and achieved complete remission following 6 cycles of R-CHOP-like chemotherapy. Patients with CNS disease at diagnosis or not achieving complete remission with standard chemotherapy were excluded from analysis.

42 patients received 2 cycles of high-dose methotrexate (HD-MTX) 3g/m^2 with two additional doses of Rituximab 375mg/m^2 following completion of 6 cycles of R-CHOP chemotherapy with the intention of preventing CNS relapse.

Cell of origin was evaluated by modified Choi criteria[5].

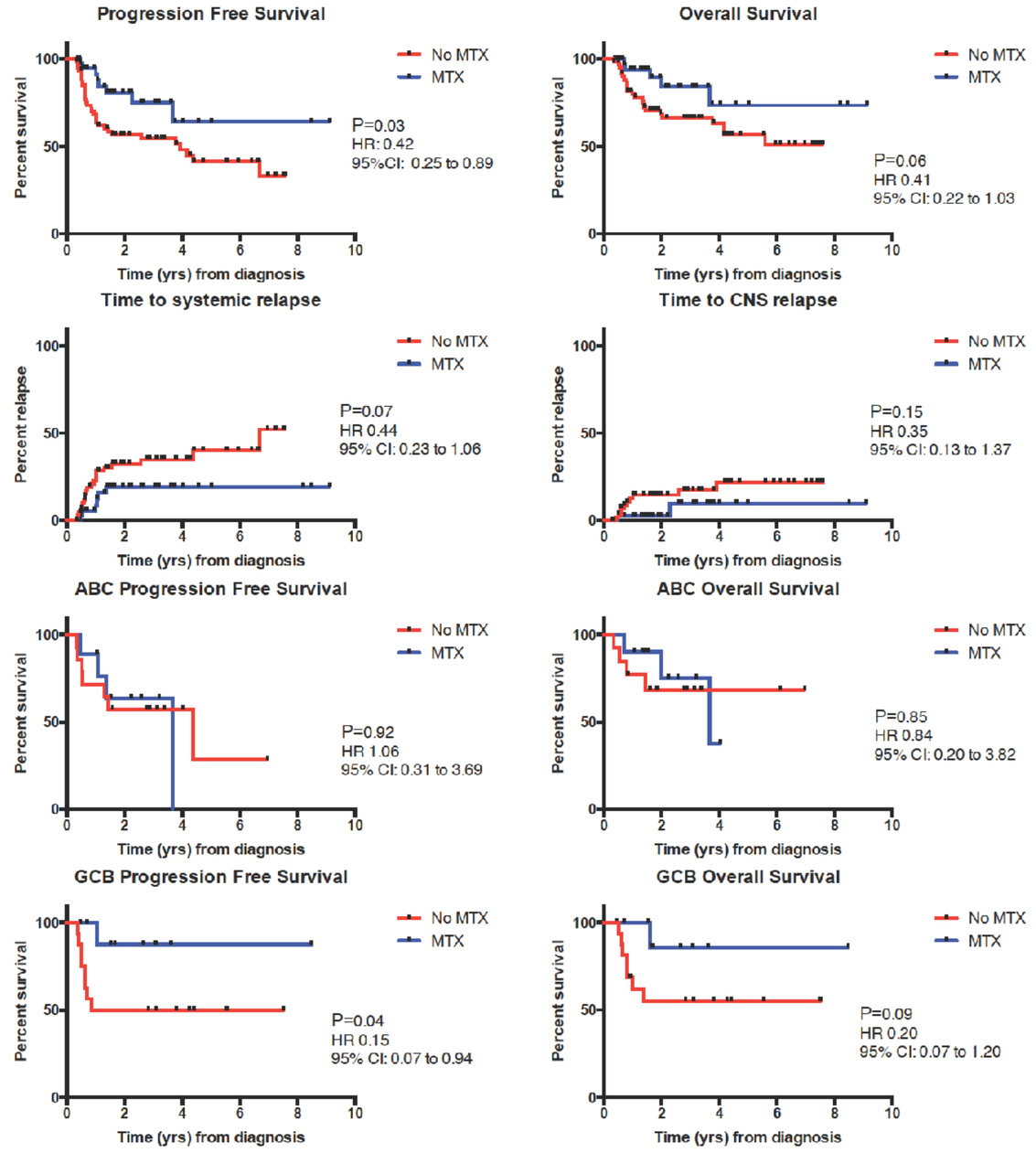
Results

Baseline Characteristics		Control n=62	HD-MTX n=42	Total n=104	P value*
Median age (Range)		72 (41-89)	66 (33-81)	71 (33-89)	0.03
Male		39 (63%)	22 (52%)	61 (59%)	0.32
Median follow-up in surviving patients (months)		43.2	27.6	36.0	0.01
Age >60		53 (85%)	32 (76%)	85 (82%)	0.30
Stage 3 or 4		54 (87%)	41 (98%)	95 (91%)	0.08
B symptoms		14 (23%)	23 (52%)	36 (35%)	0.01
LDH elevated		46 (74%)	36 (86%)	82 (79%)	0.22
R-IPI	3	33 (53%)	13 (31%)	46 (44%)	0.03
	4	21 (34%)	24 (57%)	45 (43%)	0.03
	5	8 (13%)	5 (12%)	13 (13%)	0.99
High risk for CNS relapse (high risk site or ≥2 extranodal sites)		42 (66%)	40 (95%)	82 (79%)	<0.01
Transformed from previous indolent histology		5 (8%)	10 (23%)	15 (15%)	0.01
Modified Choi cell of origin	Activated B-cell (ABC)	13 (21%)	10 (24%)	23 (22%)	0.81
	Germinal Centre B-cell (GCB)	16 (26%)	11 (26%)	27 (26%)	0.99
	Indeterminate	2 (3%)	2 (5%)	4 (4%)	0.69
	Unavailable#	31 (50%)	19 (45%)	50 (48%)	0.99

* t-test for parametric and Mann-Whitney test for non-parametric variables
# inadequate tissue available, unable to obtain specimen, not yet performed

Results (con't)

Survival and relapse outcomes	CONTROL n=62	HD-MTX n=42	HR	P value
2 year OS (%)	66%	84%	0.47	0.06
2 Year PFS (%)	56%	81%	0.46	0.02
Systemic relapse	28 (45%)	7 (16%)	0.49	0.07
CNS relapse	17 (27%)	3 (6%)	0.42	0.15



The regimen was generally well tolerated with a single patient experiencing grade 3 renal toxicity which prevented administration of the subsequent cycle, and six patients experiencing grade 2 mucositis.

Conclusion

The use of consolidative HD-MTX is associated with improved OS and PFS in patients with poor-risk DLBCL, including the elderly. This appears mainly due to a reduction in both CNS and systemic relapse. However the benefit could only be identified in those with the IHC-defined GCB subtype.

In contrast, the GELA group recently reported improved outcomes in ABC-type DLBCL with the intense HD-MTX containing ACVBP regimen[6]. This difference is unexplained but may be attributable to the exclusion of patients that failed to achieve remission with R-CHOP (mainly ABC-DLBCL) from our series. While cell of origin has been shown to influence response to novel agents, its impact on responses to standard chemotherapeutic agents is less well defined. Further prospective studies examining differential responses to chemotherapy agents by cell of origin are warranted.

Disclosure

Nothing to declare

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Aggressive B-cell lymphoma

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