Efficacy of intravenous high-dose methotrexate in preventing relapse to the central nervous system in R-CHOP(-like)-treated, high-risk, diffuse large B-cell lymphoma patients and its effect on mortality: a systematic review and meta-analysis

Elisabeth R. Tolley,[1] Christian Lewinter,[2] Lars M. Pedersen[3,4] and Torsten Holm Nielsen[1,3,5]

[1]Department of Hematology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark; [2]Karolinska University Hospital, Heart Center, Stockholm, Sweden; [3]Department of Hematology, Zealand University Hospital, Roskilde, Denmark; [4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark and [5]Danish Medicines Agency, Copenhagen, Denmark

Correspondence: T. H. Nielsen
torsten.holm.nielsen@gmail.com

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Supplementary table 1. Search strategy and data collection.

Search strategy for "Efficacy of intravenous high-dose methotrexate in preventing relapse to the central nervous system in R-CHOP(-like) treated, high-risk, diffuse large B-cell lymphoma patients and its effect on mortality: a systematic review and meta-analysis"

18.5.2022

PubMed:

Time limit: 2000-current

#1

Methotrexate"[Mesh] OR

Methotrexate[Title/Abstract] OR

MTX[Title/Abstract] OR

CNS prophylaxis[Title/Abstract] OR

antineoplastic combined chemotherapy protocols[MeSH Terms]

2

"Lymphoma, Large B-Cell, Diffuse"[Mesh] OR

Diffuse Large B-Cell Lymphoma[Title/Abstract] OR

DLBCL[Title/Abstract]

3

Central Nervous System Neoplasms"[Mesh])

OR (Central nervous system relapse[Title/Abstract]))

OR (CNS relapse[Title/Abstract]

Final search:

#1 AND #2 AND #3 = 426

UPDATED PubMED 01-03-2023

((("2022/05/08"[Date - Create] : "3000"[Date - Create])) OR (("2022/05/08"[Date - Entry] : "3000"[Date - Entry]))) OR (("2022/05/08"[Date - MeSH] : "3000"[Date - MeSH]))

Results: 26

EMBASE 18.5.22

Time limit: 2000-current

#1

methotrexate/

OR

methotrexate.mp.

OR

MTX.mp.

#2

exp diffuse large B cell lymphoma/

OR

diffuse large B cell lymphoma.mp.

OR

DLBCL.mp.

#3

exp central nervous system tumor/

OR

exp *central nervous system/

OR

((Central nervous system or CNS) adj6 relapse*).mp.

Final search:

#1 AND #2 AND #3 = 1227

Embase <1974 to 2022 May 17>

1	methotrexate/	194799
2	methotrexate.mp.	200775
3	MTX.mp.	27307
4	exp central nervous system tumor/	365667
5	((Central nervous system or CNS) adj6 relapse*).mp.	4338
6	exp *central nervous system/	753829
7	4 or 5 or 6	1101623
8	exp diffuse large B cell lymphoma/	20637
9	diffuse large B cell lymphoma.mp.	35538
10	DLBCL.mp.	21999
11	8 or 9 or 10	39049
12	1 or 2 or 3	204056
13	7 and 11 and 12	1229
14	limit 13 to yr="2000 -Current"	1227

<u>Validation process:</u>

15	("34385415" or "33811794" or "34135307" or "33881464" or "31848681" or "31222719" or "30689468" or "31115880" or "25312994").pm.	9
16	"Intravenous but not intrathecal central nervous system-directed chemotherapy improves survival in patients with testicular diffuse large B-cell lymphoma.".mp.	1
17	"32577843".pm.	1
18	14 or 17	1227
19	14 or 15 or 16 or 17	1227

Updated EMBASE search March 1st 2023

Embase <1974 to 2023 February 28>

1	methotrexate/	204813		
2	methotrexate.mp.	211073		
3	MTX.mp.	29034		
4	exp central nervous system tumor/	409587		
5	((Central nervous system or CNS) adj6 relapse*).mp.	4621		
6	exp *central nervous system/	791210		
7	4 or 5 or 6	1181332		
8	exp diffuse large B cell lymphoma/	24733		
9	diffuse large B cell lymphoma.mp.	39678		
10	DLBCL.mp.	24016		
11	8 or 9 or 10	43425		
12	1 or 2 or 3	214673		
13	7 and 11 and 12	1364		
14	limit 13 to yr="2000 -Current"	1362		
15	limit 13 to dc="20220508-20230301"	130		
16	limit 13 to rd="20220508-20230301"	99		
17	15 or 16	133		

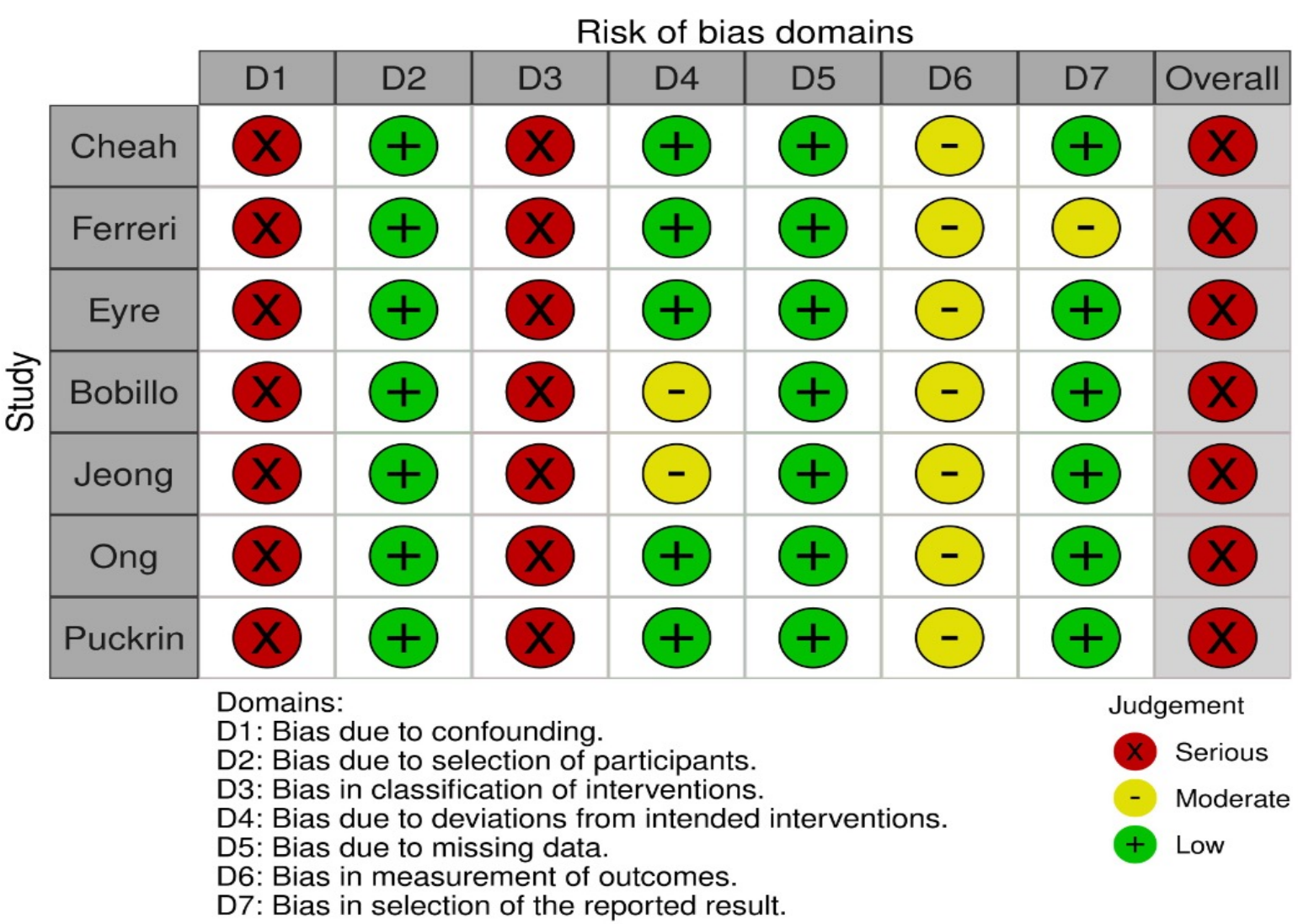
Data collection for "Efficacy of intravenous high-dose methotrexate in preventing relapse of Diffuse Large B-cell Lymphoma to the central nervous system: a systematic review and meta-analysis"

The extracted data included number of CNS relapses (events) and number of included patients in the intervention and the control group, respectively. Survival data were noted when available. We extracted "background data" on publication year, study design, patient population, age, sex, follow-up time, CNS-specific diagnostic work-up, first-line treatment, risk stratification method, criteria for using CNS prophylaxis and HD-MTX dose.

Supplementary table 2. PICO module of the research question

Patients	Intervention	Comparator	Outcome
DLBCL-patients, high risk of CNS relapse, age ≥18, first-line treatment of R-CHOP or similar regimens. No CNS-involvement up front.	Addition of intravenous MTX to standard first-line treatment.	No CNS prophylaxis or IT prophylaxis.	Primary ourcome: CNS relapse. Secondary outsome: Overall survival irrespective of CNS relapse.

Supplementary table 3: Risk of bias estimation by use of the ROBINS-I tool



Supplementary table 4. GRADE assesment of the body of evidence

GRADE										
No. of studies	Outcome	Domains that can lower certainty					Domains that can increase certainty			
		Risk of bias	Heterogeneity	Indirectness	Imprecision	Publication bias	Large effect	Dose response	Opposing plausible residual bias or confounding	GRADE rating
7	Relapse	Serious	Serious	Not serious	Serious	Not serious	No	No	No	Low
5	Survival	Serious	Serious	Not serious	Serious	Not serious	No	No	No	Low

Author(s): Elisabeth Reuben Tolley
Question: HD-MTX as CNS-prophylaxis compared to IT or no CNS-prophylaxis in DLBCL-patients deemed at high risk of CNS-relapse
Setting: Hospital
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HD-MTX as CNS-prophylaxis	IT or no CNS-prophylaxis	Relative (95% CI)	Absolute (95% CI)		
CNS relapse												
7	observational studies	serious[a]	serious[b]	not serious	serious[c]	all plausible residual confounding would reduce the demonstrated effect	38/452 (8.4%)	125/1209 (10.3%)	**RR 0.54** (0.27 to 1.07)	**48 fewer per 1.000** (from 75 fewer to 7 more)	⨁⨁◯◯ Low	CRITICAL
Mortality												
5	observational studies	serious[a]	serious[d]	not serious	serious[c]	all plausible residual confounding would reduce the demonstrated effect	107/379 (28.2%)	225/567 (39.7%)	**RR 0.70** (0.44 to 1.11)	**119 fewer per 1.000** (from 222 fewer to 44 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Based on the etsimation of "serious risk" in two out of seven domains: "Bias due to confounding" and "Bias in classification of interventions".
b. I^2= 61% corresponding to substabtial heterogeneity
c. A relatively low number of events and results wide confidence intervals
d. I^2 = 73% corresponding to substabtial heterogeneity

Supplementary table 5. Requests for supplementary data and data provided

Paper	Request	Response	No of potential patients	Outcome of study as published
Guirguis et al, 2012 DOI: 10.1111/j.1365-2141.2012.09247	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis	Not possible to provide the requested data	17 HD-MTX +/- IT, 10 IT-MTX alone (CNS prophylaxis = 27, no prophylaxis = 187)	HD-MTX was not associated with reduction in the risk of CNS relapse.
Kumar et al, 2012 DOI: 10.1002/cncr.26588	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis	Not possible to provide the requested data	33 HD-MTX, 84 IT-MTX (CNS prophylaxis = 117, no prophylaxis = 872)	HD-MTX was not associated with reduction in the risk of CNS relapse.
El-Galaly et al, 2017 DOI: 10.1016/j.ejca.2016.12.029	Summary statistics requested for high risk patients solely receiving HD-MTX as systemic prophylaxis (excluding those receiving HD-cytarabine)	Not possible to provide the requested data	65 CNS-IPI high risk patients with systemic prophylaxis (26 only systemic, 39 both systemic and IT), 292 CNS-IPI high risk patients without systemic prophylaxis	HD-MTX was not associated with reduction the risk of CNS relapse
Kansara et al, 2017 DOI: 10.1111/bjh.14229	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis	Not possible to provide the requested data	12 HD-MTX, 36 IT-prophylaxis (CNS-prophylaxis = 48, no prophylaxis = 1684)	Association between prophylaxis and CNS relapse not reported
Goldschmidt et al, 2019 DOI: 10.1080/10428194.2018.1564823	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis (restricted to patients receiving rituximab)	Not possible to provide the requested data	130 HD-MTX, 350 no HD-MTX . IT MTX to 35 ppt, distribution unknown	HD-MTX was not associated with reduction of the risk of CNS relapse, but an improved PFS/OS was found in the HD-MTX treated group
Kuitunen et al, 2020 DOI: 10.1007/s00277-020-04140-0	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis (restricted to patients with DLBCL)	Not possible to provide the requested data	57 HD-MTX + IT-MTX, 38 without CNS-prophylaxis	HD-MTX was associated with reduction of the risk of CNS relapse
Wang et al, 2020 DOI: 10.1002/ajh.25723	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis (excluding patients who went on to ASCT)	Not possible to provide the requested data	90 HD-MTX, 91 IT prophylaxis (Auto-HSCT: control: 15, intervention: 20)	HD-MTX was associated with reduction of the risk of CNS relapse
Faqah et al, 2021 DOI: 10.1200/GO.20.00422	Summary statistics (relapse rate and OS/PFS) for patients specifically receiving Rituximab	Not possible to provide the requested data	64 HD-MTX + IT MTX (+ HSCT), 46 IT-MTX	HD-MTX was not associated with reduction of the risk of CNS relapse
Harrysson et al, 2021 DOI: 10.1038/s41408-020-00403-1	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX +/- IT vs no systemic prophylaxis +/- IT (excluding those receiving HD-cytarabine)	Not possible to provide the requested data	246 systemic prophylaxis +/- IT (93+153), 2927 no CNS-prophylaxis	Association between prophylaxis and CNS relapse not reported
Orellana-Noia et al, 2022 DOI: 10.1182/blood.2021012888	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis (specifically R-CHOP treated)	Not possible to provide the requested data	IV prophylaxis 236, IT prophylaxis 894	HD-MTX was not associated with reduction of the risk of CNS relapse
Included studies				
Cheah et al, 2014 (28) DOI: 10.1038/bjc.2014.405	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis (specifically R-CHOP treated)	Requested data provided	HD-MTX: 10/122 (8,1%) Controls: 4/10 (40%) 5Y OS: HD-MTX: 96/122 (78%) Controls: 5/10 (50%)	HD-MTX was associated with reduction of the risk of CNS relapse
Jeong et al, 2021 (29) DOI: 10.1182/bloodadvances.2020003947	Summary statistics (OS/PFS) requested for patients receiving HD-MTX (those patients who actually received HD-MTX)	Requested data provided	HD-MTX: 14/114 (12%) Controls: 17/130 (13%) 5Y OS: HD-MTX: 79/144 (69.2%). Controls: 80/130 (61.9%)	HD-MTX was not associated with reduction of the risk of CNS relapse
Puckrin et al, 2021 (30) DOI: 10.1002/ajh.26181	Summary statistics (relapse rate and OS/PFS) requested for patients receiving R-CHOP or similar (R-CHOP/R-CEOP/EPOCH-R and did not receive upfront autotransplant).	Requested data provided	HD-MTX: 8/44 (18%) Controls: 25/193 (13%) 5Y OS: HD-MTX: 22/44 (50%) Controls: 116/193 (60%)	HD-MTX was not associated with reduction of the risk of CNS relapse