Supporting Document - CNS Prophylaxis in Diffuse Large Cell Lymphoma

Background

Definition

Isolated central nervous system (CNS) relapse of diffuse large B-cell lymphoma (DLBCL) is a serious and potentially fatal complication of the disease. Delivery of chemotherapy with adequate CNS penetration as part of primary therapy provides an opportunity to prevent this complication. However, there is no universally agreed approach to CNS prophylaxis and there are open questions with respect to patient selection and prophylaxis choice. Nevertheless, appropriate CNS prophylaxis during primary therapy for DLBCL should be considered in patients with recognised risk factors for CNS relapse.

This guidance document summarises risk factors for CNS relapse and provides an approach to patient selection and prophylactic treatment.

Patient selection

Until recently, much of the data used to define groups at high risk of CNS relapse antedated modern immunohistochemical diagnostic algorithms, PET-staging techniques, and the advent of routine chemoimmunotherapy with rituximab. Across all series, several or all factors in the IPI or R-IPI have conferred increased risk of CNS relapse.[1,2,3,4,5,6] The German High-Grade Lymphoma Study Group performed a retrospective analysis of prospectively collected data from clinical trials performed by their network. All patients had received chemo-immunotherapy.[7,8] The following factors were identified as predictive of isolated CNS relapse:

Each risk factor in the IPI:

- age >60
- stage III/IV disease
- raised LDH
- multiple extranodal sites (renal and/or adrenal involvement are independent risk factor)
-

performance status >1These findings were validated in an independent cohort analysed by the BCCA.[7,8]

The following risks of CNS relapse were reported:

Number of Factors	Risk of CNS relapse (German Cohort n=2164)	Risk of CNS relapse (BCCA Cohort n=1597)
0-1	0.6%	0.8%
2-3	4.1%	3.9%
4-5	17%	12%

Some caution is required to when incorporating these data into patient counselling and treatment decisions as it is yet (January 2016) to appear in peer-reviewed literature. However two reputable research groups have reported the initial and confirmatory data in international conference forums, we believe the overall message of with respect to the identification of patients with general factors predicting CNS relapse can be accepted. Further detailed analyses are awaited.

Specific sites of disease involvement lead to increasing risk of CNS relapse. The BCCA and German cohorts did not identify specific sites of disease as high risk apart from **renal or adrenal involvement.**

Based on the published cohorts enriched with extranodal disease at specific locations, the following additional extranodal sites should be considered as high risk for CNS relapse:[9,10]

- testicular[11]
- intra-ocular
- base of skull
- breast
- epidural
- Naso-pharyngeal

Isolated large cell involvement of the bone marrow is not considered independently high risk for CNS disease, but typically marrow involvement is associated with other risk factors.[10]

Biological subtypes warranting consideration of CNS prophylaxis

Double hit lymphoma: DLBCL that co-expresses MYC and BCL2 (or BCL6) by immunohistochemistry confers a risk of CNS relapse of between 9 and 17%.[12] "Double/ triple-hit" lymphoma demonstrating rearrangements of MYC and BCL2 by FISH have a similar risk of CNS relapse with a large series reporting a 13% of CNS relapse.[13]

Intravascular lymphoma: CNS involvement is common at baseline in this disease (up to 39%) and CNS prophylaxis is recommended.[14]

Choice of Prophylaxis Regimen

There is no agreed standard approach to CNS prophylaxis. Intrathecal chemotherapy with methotrexate long been a component of CNS prophylaxis and is beneficial in patients with testicular lymphoma.[15] However in other forms of DLBCL efficacy of IT MTX is uncertain. Use of CNS-penetrating intravenous antimetabolite or purine analogue therapy (methotrexate or cytarabine) has become increasingly popular globally in patients thought to be at high risk of CNS disease. Such an approach is thought to be more effective at preventing parenchymal relapse than IT Mtx In the pre-rituximab era. However prospective, controlled data are rare. Observations from a pre-rituximab, French, randomised study of intensive combination chemotherapy (ACVBP) incorporating 2 cycles of 3 g/m^2 methotrexate versus CHOP with no CNS directed therapy showed a significantly lower risk of CNS relapse.[16] A local, multicentre, retrospective study of 269 patients explored three approaches to CNS prophylaxis (IT MTX alone with R-CHOP-like chemotherapy; IT MTX + IV MTX 3 g/m^2 x2 doses with R-CHOP-like chemotherapy; regimens containing high doses of ara-C and MTX [CODOX-M/IVAC or HyperCVAD] and found CNS relapse rates of 18.4%, 6.9% and 2.3% (p=0.006).[17]

Management

Patient Selection Recommendations:

- careful staging for CNS involvement at baseline with a diagnostic lumbar puncture and MRI in patients with DLBCL 4-5 risk factors.
- the routine use of systemic CNS prophylaxis, where patient factors allow, for patients with 4 or more of the above IPI risk factors, or high risk sites for CNS relapse of disease involvement.
- consideration of systemic CNS prophylaxis in patients where 2-3 IPI risk factors are present, based on physician preference and relative toxicities of the prophylaxis in individual patients.

Prophylaxis Recommendations:

In the absence of high quality evidence, it is not possible to recommend one protocol for CNS prophylaxis over another. Patient factors may limit the deliverability of high dose methotrexate, and high dose methotrexate should be delivered by physicians familiar with its use, and who have access to a laboratory capable of reporting methotrexate levels rapidly.

The following approaches to systemic prophylaxis should be considered:

- 2-4 cycles of methotrexate 3g/m2 during or post completion of induction chemotherapy (typically R-CHOP) (18, 19)

- intercalation of methotrexate within R-CHOP at approximately day 10 of the first 2 cycles
- a specific approach to CNS prophylaxis may not be required in patients receiving regimens containing CNS-penetrating agents such as hyperCVAD or CODOX-M/IVAC
- for patients with testicular DLBCL, CNS prophylaxis requires the use of both IT MTx and IV MTx with chemotherapy, together with irradiation of the contralateral testicle.

References

1. Boehme, V., N. Schmitz, S. Zeynalova, et al. 2009. "CNS events in elderly patients with aggressive lymphoma treated with modern chemotherapy (CHOP-14) with or without rituximab: an analysis of patients treated in the RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL)." Blood 113(17):3896-3902.
2. Bernstein, S. H., J. M. Unger, M. Leblanc, et al. 2009. "Natural history of CNS relapse in patients with aggressive non-Hodgkin's lymphoma: a 20-year follow-up analysis of SWOG 8516 -- the Southwest Oncology Group." J Clin Oncol 27(1):114-119.
3. Hollender, A., S. Kvaloy, O. Nome, et al. 2002. "Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model." Ann Oncol 13(7):1099-1107.
4. Haioun, C., C. Besson, E. Lepage, et al. 2000. "Incidence and risk factors of central nervous system relapse in histologically aggressive non-Hodgkin's lymphoma uniformly treated and receiving intrathecal central nervous system prophylaxis: a GELA study on 974 patients. Groupe d'Etudes des Lymphomes de l'Adulte." Ann Oncol 11(6):685-690.
5. Van Besien, K., C. Ha, S. Murphy, et al. 1998. "Risk Factors, Treatment, and Outcome of Central Nervous System Recurrence in Adults With Intermediate-Grade and Immunoblastic Lymphoma" Blood 91(4) 1178 - 1184
6. Schmitz, N., S. Zeynalova, B. Glass, et al. 2012. "CNS disease in younger patients with aggressive B-cell lymphoma: an analysis of patients treated on the Mabthera International Trial and trials of the German High-Grade Non-Hodgkin Lymphoma Study Group." Ann Oncol 23(5):1267-1273.
7. Savage, K. J., S. Zeynalova, R. R. Kansara, et al. 2014. "Validation of a Prognostic Model to Assess the Risk of CNS Disease in Patients with Aggressive B-Cell Lymphoma" Blood 2014 - Am Soc Hematology
8. Schmitz, N., S. Zeynalova, M. Nickelsen, et al. 2013. "A new prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma." Hematological Oncology 31:96-150.
9. Cheah, C. Y. and J. F. Seymour. 2015. "Central nervous system prophylaxis in non-Hodgkin lymphoma: who, what, and when?" Curr Oncol Rep 17(6):25.
10. Cheah, C. Y., Seymour, J., Dickinson, M. 2014. "Ongoing challenge of optimal patient selection for CNS prophylaxis in patients with non-Hodgkin lymphoma" Int.J.Hematol.Oncol. 3(3):189-201.
11. Cheah, C. Y., A. Wirth and J. F. Seymour. 2014. "Primary testicular lymphoma." Blood 123(4):486-493.
12. Savage, K. J., L.H. Sehn, D. Villa, et al. 2014. "The Impact of Concurrent MYC BCL2 Protein Expression on the Risk of Secondary Central Nervous System Relapse in Diffuse Large B-Cell Lymphoma (DLBCL)." Blood 124:495-495
13. Oki, Y., M. Noorani, P. Lin, et al. 2014. "Double hit lymphoma: the MD Anderson Cancer Center clinical experience." Br J Haematol 166(6):891-901.
14. Ferreri, A. J., E. Campo, J. F. Seymour, et al. 2004. "Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'." Br J Haematol 127(2):173-183.

15. Vitolo, U., A. Chiappella, A. J. Ferreri, et al. 2011. "First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial." J Clin Oncol 29(20):2766-2772.
16. Tilly, H., E. Lepage, B. Coiffier, et al. 2003. "Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma." Blood 102(13):4284-4289.
17. Cheah, C. Y., K. E. Herbert, K. O'Rourke, et al. 2014. "A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma." Br J Cancer 111(6):1072-1079.
18. Abramson, J. S. and E. Hochberg. 2011. "Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in highrisk patients with diffuse large Bcell lymphoma." Cancer 117(10) [Correspondence]
19. O'Rourke, K., K. Morris and G. A. Kennedy. 2010. "Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in highrisk patients with diffuse large Bcell lymphoma." Cancer. 117(10)[Correspon**dence]**