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Incidence and risk factors of central nervous system recurrence in aggressive lymphoma—a survey of 1693 patients treated in protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) FREE

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Annals of Oncology, Volume 18, Issue 1, 1 January 2007, Pages 149–157,
<https://doi.org/10.1093/annonc/mdl327>

Published: 03 October 2006 **Article history** ▼

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Abstract

Background: Central nervous system (CNS) relapse is a devastating and usually fatal complication of aggressive lymphoma. The extent of the disease, the proliferation rate and the sites of extranodal involvement have been discussed as risk factors. We analyzed the patients treated on protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) between 1990 and 2000, evaluated the rate and prognostic factors for CNS recurrence and developed a risk model trying to identify subsets of patients suitable for future prophylactic strategies.

Patients and methods: From 1993 to 2000, 1399 patients [≥ 60 years with normal lactate dehydrogenase (LDH) and >60 years irrespective of LDH] were randomized to receive six cycles of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-21, CHOP-14 or six cycles of CHOP + etoposide (CHOEP)-21, CHOEP-14 in a 2×2 factorial study design in the NHL-B1/B2 studies. From 1990 to 1997, 312 patients ≥ 60 years with an elevated LDH were randomized to five cycles CHOEP + involved field (IF) radiotherapy or three cycles CHOEP followed by high-dose BCNU, etoposide, cytarabine and melphalan (BEAM) and autologous stem-cell transplantation (NHL-A study).

Results: A total number of 1711 patients were initially eligible for this study, of whom 18 patients had to be excluded due to primary CNS involvement. In the remaining 1693 assessable patients, 37 cases of relapse or progression to the CNS (2.2%) were observed. The protocol asked for an intrathecal

(i.th.) prophylaxis in patients with lymphoblastic lymphoma only ($n = 17$), but overall 71 patients (71 of 1693 = 4.2%) received prophylaxis by decision of the treating physicians. Multivariate Cox regression analysis identified increased LDH ($P < 0.001$) and involvement of more than one extranodal site ($P = 0.002$) as independent predictors of CNS recurrence in the NHL-B1/B2 study population. Treatment with etoposide also evolved as a prognostic factor because the risk of CNS failure was significantly reduced after CHOEP ($P = 0.017$). Elderly patients presenting with both an elevated LDH and lymphoma involvement in liver, bladder or adrenals had an up to 15-fold risk of spread of the disease to the CNS.

Conclusion: The incidence of CNS relapse in 1693 patients treated for aggressive lymphomas on DSHNHL protocols from 1990 to 2000 was low (2.2%), although CNS prophylaxis was administered to <5% of patients. Thus, a general prophylaxis for all patients is not warranted, the less so since the effectiveness of i.th. prophylaxis itself is judged controversially. Increased LDH and involvement of more than one extranodal site were confirmed as independent risk factors. A cumulative 20% incidence of CNS disease in certain prognostic subgroups of elderly patients may render these candidates for i.th. prophylaxis; however, this approach would imply a potential overtreatment of 80% of these patients deemed at high risk.

Keywords: [aggressive lymphoma](#), [CNS recurrence](#), [prognostic factors](#), [prophylaxis](#)

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