New risk factors and new tendency for central nervous system relapse in patients with diffuse large B-cell lymphoma

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Background: Central nervous system (CNS) relapse in patients with diffuse large B cell lymphoma occurs uncommonly, but is always fatal[1]. Detection of reliable risk factors for CNS relapse is still an open question[2]. Role of rituximab and intrathecal (IT) prophylaxis remains controversial[3-4].We aimed to retrospectively explore the risk factors for CNS relapse in entire cohort and R-CHOP set, and evaluate the efficacy of rituximab and IT prophylaxis for CNS relapse reduction. **Method**: 511 patients with newly diagnosed DLBCL treated at the Sun Yat-sen University Cancer Center from January 2003 to December 2012 were included in the study.376 patients (73.6%) received R-CHOP as primary treatment, and the remaining 135 patients received CHOP instead. IT prophylaxis was administered to those who were deemed at high risk of CNS relapse including those with bulky mass, high level of ki-67 and involvement of specific extranodal sites (e.g. testis, breast and kidney). It consisted of 15mg methotrexate and 50mg cytarabine performed by lumbar puncture on the first day of each cycle. In the entire cohort and R-CHOP set, Kaplan-Meier method with log-rank test was used for univariate analyses and Cox proportional hazards model was used for multivariate analysis. Differences were evaluated using a two-tailed test, $p<0.05$ was considered as statistically significant. **Result**: At a median follow-up of 46 months, 25 patients (4.9%) experienced CNS relapse. There was a trend to reduced likelihood of CNS disease in patients treated with rituximab, the 3 years cumulative incidences of CNS relapse were 2.7% and 7.1% in R-CHOP and CHOP set, respectively($p=0.045$).

Addition of IT prophylaxis did not confer much benefit to CNS relapse in both entire cohort and R-CHOP set. In multivariate analysis, involvement of bone (RR=4.21, 95% CI= 1.38 to 12.77), involvement of kidney (RR=3.85, 95% CI= 1.05 to 14.19), alkaline phosphatase （ALP） >110u/L (RR=3.59, 95% CI= 1.25 to 10.34), serum albumin（ALB）<35g/L (RR=3.63, 95% CI= 1.25 to 10.51), treated with rituximab (RR=0.34, 95% CI= 0.12 to 0.96), and time to complete remission <108 days (RR=0.22, 95% CI= 0.06 to 0.78) were each independently predictive of CNS relapse in entire cohort. Involvement of bone (RR=4.44, 95% CI= 1.08 to 18.35), involvement of bone marrow (RR=11.70, 95% CI= 2.24 to 60.99) and involvement of kidney (RR=10.83, 95% CI= 2.27 to 51.65) were independent risk factors of R-CHOP set. **Conclusion:** Rituximab can decrease the incidence of CNS relapse, while IT prophylaxis alone may not be sufficient in reducing CNS occurrence. ALB, ALP and time to complete remission are new independent risk factors for predicting CNS relapse in whole cohort. When restricted to patients treated with R-CHOP, there is a new trend of increased risk for those with specific extranodal sites involvement.

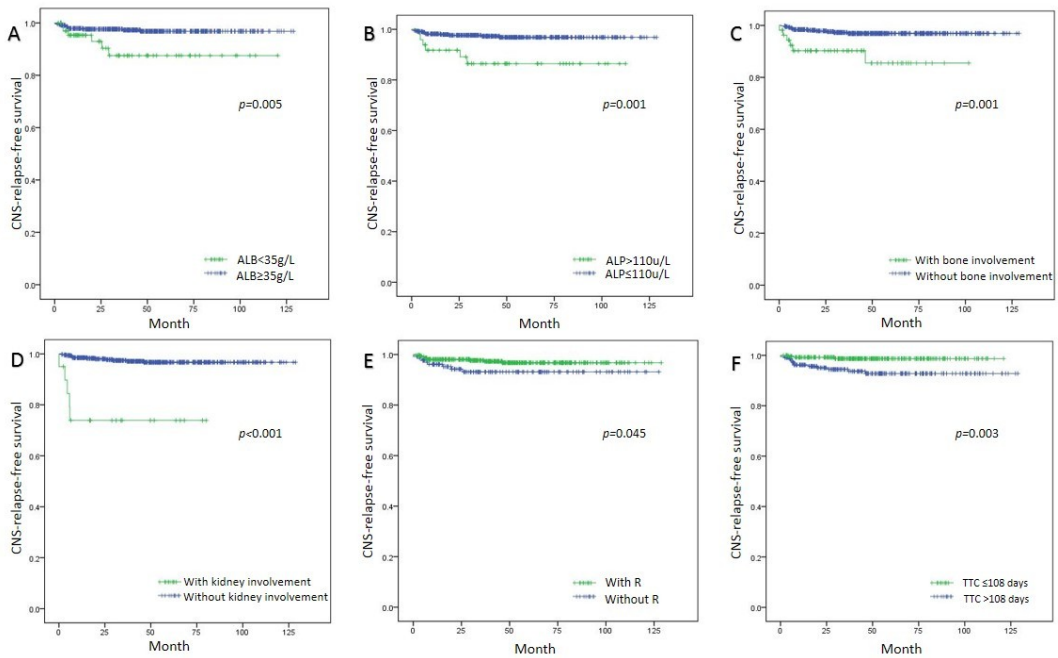

Figure 1.Kaplan-Meier estimated CNS-relapse-free survival for independent risk factors of entire cohort.

Abbreviation: CNS, central nervous system; ALB, albumin; ALP, alkaline phosphatase ;R, rituximab; TTC, time to complete remission.

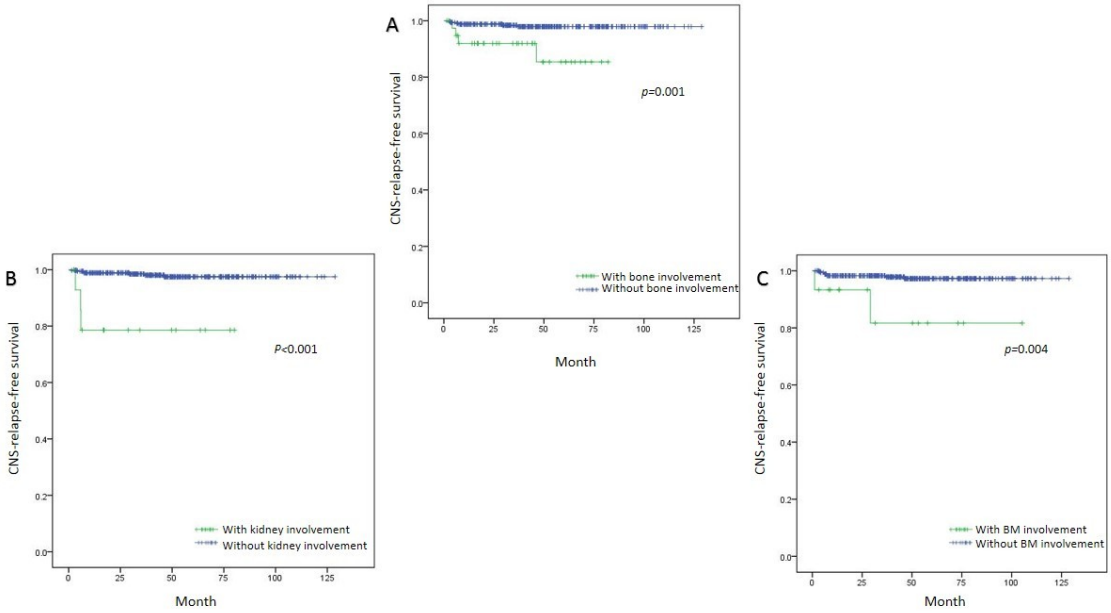

Figure 2.Kaplan-Meier estimated CNS-relapse-free survival for independent risk factors of R-CHOP set.
Abbreviation: CNS, central nervous system; BM, bone marrow.

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