BCL2 Expression and BCL2/MYC Dual Expression Predicts Inferior Survival in Primary Central Nervous System Lymphoma

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BACKGROUND

Primary CNS lymphoma (PCNSL) is a rare type of diffuse large B-cell lymphoma (DLBCL) arising from and usually confined to CNS. Understating of the pathogenesis and prognostic markers is a challenge due to rarity of this neoplasm and paucity of the material available to study. Recent studies have shown that dual expression of MYC and BCL2 in DLBCL contributes to inferior overall survival. The prognostic value of MYC and BCL2 in PCNSL is not well studied.

MATERIALS AND METHODS

A retrospective analysis of 30 cases of PCNSL was performed. Immunohistochemistry for MYC (clone Y69) and BCL2 (clone 124) and chromogenic in situ hybridization (CISH; MYC DNP probe) for MYC (All from Ventana Medical Systems) were performed. Overexpression of MYC and BCL2 was defined if >40% and >80% tumor cells were positive for MYC and BCL2 respectively. Amplification of MYC gene was defined if MYC/cen8 signal ratio ≥2. The cut-off values were decided after careful review of literature. MYC, BCL2 expression and MYC amplification were correlated with overall survival (OS) using Kaplan-Meier survival analysis. Association of MYC expression and MYC amplification was analyzed using Fisher’s exact test.

RESULTS

All 30 patients had primary CNS DLBCL with no systemic involvement at the time of diagnosis. The treatment included methotrexate with or without radiation followed by rituximab.

1. MYC amplification, MYC overexpression and BCL2 overexpression were detected in 16.6% (n=5), 50% (n=15) and 53.3% (n=16) patients respectively.
2. Dual expression of MYC and BCL2 was present in 30% (n=9) patients.
3. Patients with BCL2 overexpression or BCL2/MYC dual expression had significantly shorter OS (p=0.01, p=0.038 respectively).
4. Neither MYC overexpression nor MYC amplification alone was associated with the difference in OS (p=0.296, p=0.939 respectively).
5. There was no correlation between MYC amplification and MYC overexpression (p=0.330).

DISCUSSION

The prognostic value of many immunohistochemical and molecular markers is unclear in PCNSL. Chang et al have previously reported poor prognosis in patients with expression of p53, BCL6 and/or c-MYC. Brunn et al reported that frequent triple expression of MYC, BCL2 and BCL6 and the absence of MYClow and BCL2high subgroup may underlie the inferior survival in PCNSL. In contrast to the previous studies, we found no prognostic value on either MYC expression or MYC amplification. There was no statistically correlation between MYC expression and MYC amplification, indicating that MYC expression was through a different mechanism other than gene amplification. Assanasen et al have reported similar results in 25 patients with PCNSL.

Another interesting finding from the current study is that patients with BCL2 expression have more significant survival difference as compared to patients with co-expression of BCL2 and MYC. This is in contrast to the systemic DLBCL in which BCL2/MYC dual expression, rather than BCL2 alone, contributes to worse prognosis. BCL2 is an anti-apoptotic protein that contributes to prolonged cell survival in low grade lymphomas. BCL2 over-expression may result from different mechanisms such as translocation, amplification etc. A few studies have previously reported BCL2 as poor prognostic marker in systemic DLBCL, activated B-cell type. Since most PCNSL lymphomas are activated B-cell type, our finding suggests that, similar to systemic DLBCL, BCL2 expression in PCNSL may contribute to worse overall survival. It is possible that BCL2 expression is surrogate marker of other underlying biology. Further study of larger numbers of cases is required to confirm our finding.

CONCLUSION

While MYC overexpression or MYC amplification alone does not indicate a poor prognosis, MYC/BCL2 dual expression or BCL2 expression predicts poor OS in primary CNS lymphoma. MYC expression does not correlate with MYC DNA amplification, suggesting that MYC expression may be caused by an alternative mechanism.

REFERENCES