Original Study

Complex Karyotype Is Associated With Aggressive Disease and Shortened Progression-Free Survival in Patients With Newly Diagnosed Mantle Cell Lymphoma

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Abstract

We evaluated the role of pretreatment cytogenetics in patients with untreated mantle cell lymphoma (MCL). Patients with ≥ 3 chromosomal abnormalities had inferior progression-free and overall survival and had more high-risk clinical features. The effect of cytogenetics merits further evaluation in prognostic assessment in MCL.

Background: Pretreatment cytogenetics are not routinely used to predict patient outcomes in mantle cell lymphoma (MCL). Based on the prognostic utility of cytogenetics in other diseases, we reviewed the effect of a complex karyotype (CK) in MCL. **Patients and Methods:** We included patients evaluated between November, 2002, and May, 2011. Those with ≥ 3 chromosomal abnormalities on a pre-treatment cytogenetic evaluation were defined as CK. Demographic, clinical, and survival differences between patients with CK and non-CK (NCK) were assessed. **Results:** Of 80 patients, 32 (40%) had CK, which was associated with high-risk clinical risk factors. Therapy did not differ between the groups, nor did rate of autologous stem cell transplant (ASCT). The 2-year progression-free survival (PFS) estimates were 70% and 48% for patients with NCK and CK, respectively ($P = .02$). Two-year overall survival (OS) estimates were also greater in those with NCK versus CK (85% vs. 58%; $P = .02$). When controlling for high-risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score ($P = .006$), bulky disease ($P = .01$), and ASCT in first remission ($P = .01$), CK was not significantly associated with PFS ($P = .18$). **Conclusion:** CK is associated with shortened PFS and OS in MCL but has not been demonstrated to be prognostic independent of other variables in this series.

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Introduction

Mantle cell lymphoma (MCL) is incurable outside of allogeneic stem cell transplantation, and median overall survival (OS) is estimated at 5 years.[1,2] There is no standard approach to risk stratification in newly diagnosed patients, for whom clinical, pathologic, and molecular markers are all used to predict outcomes. The Mantle Cell Lymphoma International Prognostic Index (MIPI) has been assessed in the transplant and nontransplant settings and is prognostic for OS.[3,4] The Ki-67 proliferative index remains a key component of risk stratification and has been assessed in several series. A Ki-67 index of > 35% was associated with inferior progression-free survival (PFS; $P < .03$) in 1 series of 52 patients and, in a second study of 134 heterogeneously treated patients, a Ki-67 of > 60% was associated with an OS of only 13 months compared with 53 months in patients with a Ki-67 of ≤ 20%.[5,6] A cutoff of 30% has also been proposed based on results of European studies.[7] Ki-67 has been combined with the MIPI

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to form the biologic MIPI (MIPIb), which also provides prognostic information beyond MIPI alone, and MIPIb has recently been validated in a review of European Mantle Cell Lymphoma Network trials. The MIPIb incorporates Ki-67 as a continuous variable.[4,8] Last, mutations involving *NOTCH1* and overexpression of SOX11 might also have prognostic implications in MCL.[9,10]

Risk stratification routinely incorporates cytogenetics using conventional karyotype analysis in many hematologic malignancies, but this is not the case in MCL in which data are more limited.[11-13] One review of 145 cases of MCL detected a complex karyotype (CK; ie, $\geq$ 3 chromosomal abnormalities including t(11;14)) in up to 41% of MCL cases but did not report the effect of CK on survival.[14] A second series demonstrated an association of structural aberrations with survival because patients with $\geq$ 4 aberrations had a median OS of 15 months compared with 36 months in the remaining patients.[15] In addition to evidence of a poor prognosis with increased number of cytogenetic abnormalities, selected cytogenetic abnormalities like del(17p) and add(3q) appear to be associated with inferior OS. Del(17p) and add(3q) were detected using conventional cytogenetics in 10% and 8% of patients, respectively, in the series of 145 patients reported by Espinet et al.[14] Four-year OS was 14% for patients with del(17p) versus 54% for those without del(17p), and 4-year OS was 0% for those with add(3q) versus 54% for those without add(3q). Both abnormalities were significantly associated with OS when adjusting for blastoid morphology ($P = .001$ for add(3q) and $P = .014$ for del(17p)).[14,15] The British Columbia Cancer Agency has identified additional recurrent cytogenetic abnormalities in a series of 214 patients with MCL treated at their center and identified in the literature, although there are no reported data on the clinical outcomes based on these abnormalities.[16] A recent multicenter series of 125 patients with MCL found that 60% of untreated patients had CK (defined as $\geq$ 3 chromosomal abnormalities), and those with CK had an inferior median OS in a multivariable analysis (hazard ratio [HR], 2.37; $P = .017$).[17]

Since 2008, cytogenetic evaluations at The Ohio State University (OSU) have incorporated stimulation with CpG oligonucleotides in patients with B-cell malignancies who undergo karyotype analysis because it increases the detection of chromosomal abnormalities in Chronic Lymphocytic Leukemia. This method of stimulation increases the number of cells with chromosomes in metaphase and identifies more abnormalities than traditional mitogens.[18] We conducted a retrospective study to determine the prognostic significance of CK in patients with previously untreated MCL.

Patients and Methods

Patients

Patients diagnosed with MCL and evaluated at OSU between November, 2002, and May, 2011, were included with follow-up through December, 2012. Patients were diagnosed using morphologic evaluation, immunohistochemistry stain for Cyclin D1, and/or fluorescence in situ hybridization (FISH) analysis for t(11;14). Pretreatment conventional cytogenetic evaluation from a bone marrow or peripheral blood sample was required. All patients with previously untreated MCL who had pathologic review and cytogenetic evaluation at OSU in addition to available clinical data were included in the analysis. Cytogenetic evaluation of nodal tissue was not available and thus not included. This retrospective review was approved by the institutional review board at OSU and informed consent was waived.

Assessment for Cytogenetic Abnormalities

Cytogenetic analysis was performed on bone marrow aspirates in 68 patients and peripheral blood in 12 patients. In 48 patients evaluated before 2008, metaphase cytogenetics were evaluated using unstimulated cultures. For the 32 remaining patients assessed beginning in 2008, stimulated cytogenetics were routinely performed using 20 µL/mL of the B-cell mitogen OSU 685, a CpG deoxyoligonucleotide (custom synthesized by Sigma-Aldrich, St Louis, MO) for 72 hours.[19] Patients with 3 or more unrelated chromosomal abnormalities, including t(11;14), were defined as having CK. Patients with $<$ 3 abnormalities were considered to have non-CK (NCK). Patient samples were also assessed for the presence of del(17p), add(3q), and other cytogenetic abnormalities in karyotype analysis. FISH was not included in this analysis.

Statistical Analysis

The primary objective of this retrospective study was to evaluate the relationship between the presence of CK and other clinical features and the prognostic effect of CK on clinical outcome in patients with untreated MCL. A secondary objective was to describe the frequency of specific abnormalities and how they associate with clinical outcome in the context of CK. Associations between CK status and categorical or continuous baseline features were tested using Fisher exact or Wilcoxon rank sum tests, respectively. Overall response rate (ORR) was defined as the percentage of patients with complete response (CR) or partial response (PR) to induction therapy and was evaluated by the treating physician using standard criteria.[20,21] PFS was calculated from the date of diagnosis until the date of relapse or death from any cause. Patients alive and relapse-free at last follow-up were censored at the time of last contact. OS was calculated from the date of diagnosis until the date of death from any cause or last follow-up. PFS and OS estimates were obtained using the method of Kaplan–Meier, and the log-rank test to evaluate differences in survival curves between groups. Proportional hazards models were fit to determine if CK provided additional prognostic information, independent of common demographic and clinical variables. MIPI risk group was defined as low (score $<$ 5.7), intermediate, and high (score $\geq$ 6.2).[4] Models were fit with variables that were at least moderately significant in univariable analyses ($P < .15$ from the likelihood ratio test). With the exception of CK, the primary variable of interest, backward selection removed the least significant variable one at a time until all other variables remaining in the final model were significant at $\alpha = 0.05$ using the Wald test. Any variables initially excluded were sequentially added back in to the model to confirm that they were not statistically significant. HRs and 95% confidence intervals (CIs) were estimated from the model.

Results

Patient Characteristics

Diagnostic characteristics of the 80 patients included in the study are presented in Table 1. Overall, the median age was 63 years (range, 37-81 years), 38% were $\geq$ 65 years of age, and 70% were