Original Study

Chronic Lymphocytic Leukemia Patients With Deletion 11q Have a Short Time to Requirement of First-Line Therapy, But Long Overall Survival: Results of a Population-Based Cohort in British Columbia, Canada

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Abstract

This study documents the clinical course of 69 patients with high-risk chronic lymphocytic leukemia (CLL) with 11q22.3 deletion (11q-), from a provincial CLL database. Aklylator-containing chemotherapies are thought to be required to overcome the adverse prognosis associated with 11q-. However, most 11q- patients did not receive alkylators first-line and had a median survival of 14.7 years, comparable with the rest of the cohort.

Background: Chronic lymphocytic leukemia (CLL) patients with 11q22.3 deletion (11q-) have an aggressive clinical course, and thus selection of first-line therapy in this group is important. This study aimed to improve our understanding of real-world practice patterns and outcomes of CLL patients with 11q- in a population-based setting. **Patients and Methods:** The British Columbia CLL Database was used to identify patients with 11q-. Overall survival (OS) and treatment-free survival (TFS) were assessed after adjustment for prognostic factors. **Results:** Of 1044 patients in the database, 125 had 11q- (12%). Sixty-nine patients had 11q- identified before therapy initiation and had a median OS and TFS of 14.7 (95% confidence interval [CI], 11.3-18.1) and 2.5 (95% CI, 1.5-3.6) years. Patient with copresence of 11q- and deletion 17p had a markedly worse prognosis, with median OS of 4.9 versus 14.7 years ($P < .001$). Most treated patients (33 of 52) received fludarabine with or without rituximab (FR). Patients treated with FR had a median OS of 12.8 years (standard error, 1.0), which was not statistically different from those treated with alkylator-containing therapy ($P = .35$). **Conclusion:** Although median TFS of 11q- patients in this cohort was short at 2.5 years, OS remains long at 14.7 years, even when most patients received initial treatment without alkylators.

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Introduction

The 11q deletion harboring the *ataxia-telangiectasia mutated (ATM)* locus at 11q22.3 (11q-) is present in up to 20% of patients with chronic lymphocytic leukemia (CLL)[1] and might be detected using fluorescence in situ hybridization (FISH) analysis. Although novel techniques such as gene expression profiling, next-generation

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sequencing, array-based comparative genomic hybridization, and single nucleotide polymorphism arrays, are increasingly used to detect genomic disturbances in CLL, in clinical practice, FISH testing remains standard of care. Also, although immunoglobulin (Ig)HV mutation status has also been shown to be a strong predictor of outcomes in CLL, many treating clinicians do not have access to this testing and FISH remains a primary method used to identify high risk patient groups.

Presence of 11q- detected using FISH is associated with development of bulky lymphadenopathy, as well as a more aggressive disease course and poor response to therapy.[2-4] Prognostic factors that might explain the variable outcome within the group of 11q- patients include percent of abnormal nuclei harboring the *ATM* deletion and presence of other cytogenetic abnormalities.[5-7] Patients with CLL 11q- with *ATM* deletions $\geq$ 25%, relative to those with $<$ 25% *ATM* deletions have been shown to have a shorter treatment-free survival (TFS).[6,8] In addition, Jain et al[8] reported that concomitant deletion of 13q (13q-) had mitigating effects on 11q-. Clonal evolution with acquisition of new genetic abnormalities during disease course has also been associated with a poor prognosis.[9] Few clinical studies have specifically focused on CLL patients with 11q- and they have been limited to single-institution and clinical trial populations. These prognostic factors have not been investigated more thoroughly in a population-based setting.

Furthermore, few clinical studies have described real-world patterns of practice within the CLL 11q- group. Because of the high-risk nature of the presence of 11q-, selection of initial therapy for this subgroup is important. Treatment recommendations have changed over time. Purine analogues became standard of care for first-line therapy after clinical trials showed superiority over chlorambucil.[10] Subsequent trials found significant improvements in response rates and progression-free survival (PFS) with the addition of cyclophosphamide to fludarabine (FC) over fludarabine (F) alone, but no significant differences in overall survival (OS).[11-13] In particular, the Leukemia Research Foundation CLL4 trial showed that patients with 11q- did as well as those without 11q- when cyclophosphamide was combined with F.[14] This and other post hoc subgroup analyses of clinical trial data led to recommendations that initial therapy of CLL patients with 11q- include cyclophosphamide.[15] There is also evidence for use of novel agents such as ibrutinib for first-line therapy of CLL patients, particularly those with high-risk features such as 11q- or deletion 17p,[16] although this therapy is not approved in all jurisdictions. Before both of these recommendations, the combination of F and rituximab (FR) became standard of care in British Columbia (BC) on the basis of a phase II trial showing superiority in PFS over a historical group of CLL patients treated with F alone.[17] The importance of the combination of rituximab (R) with first-line chemotherapy was further shown in the German CLL Study Group CLL8 trial.[18] In 2010, BC guidelines changed to recommend FC with R (FCR) for patients with 11q-; however, in real-world practice, many clinicians continued to administer FR because of its ease of administration, favorable toxicity profile, and overall outcomes.[19] This prompted us to evaluate the practice patterns among hematologists/oncologists in BC for the treatment of CLL patients with 11q- and survival outcomes on the basis of initial therapy.

Patients and Methods

The study population was identified through the BC Provincial CLL Database. In the province of BC, Canada, population 4.7 million, CLL patients receive uniform evaluation and therapy according to centrally derived standard protocols developed by the BC Cancer Agency. FISH testing is recommended for all patients before treatment to guide therapy. The BC Provincial CLL Database includes all patients who have undergone CLL-FISH testing in 1 of 3 provincial laboratories. These 3 laboratories have been validated to ensure standardization of results.[20]

All patients referred for CLL FISH testing with a confirmed 11q- at any point during the disease course between January 2004 and April 2014, when FISH testing was routinely available in BC, were included in this study. A cutoff of $>$ 10% allelic burden was used to define 11q- positivity as per our previous provincial FISH standardization.[21] A diagnosis of CLL was confirmed according to consensus guidelines[21,22] by an experienced hematopathologist after review of peripheral blood morphology and peripheral blood or bone marrow immunophenotyping. FISH analysis was performed as previously described.[20] All patients had to have had their treatment delivered in BC to be included in this study.

Overall survival from date of diagnosis, TFS (defined as time from diagnosis to treatment, death, or last follow-up), and time to second-line treatment (defined as time from first treatment to second-line treatment, death, or last follow-up) were the main outcomes of interest. These outcomes were investigated in relationship to the following prognostic factors: age ($<$ 60 vs. $\geq$ 60 years), sex, Rai stage (0-2 vs. 3-4), CD38 positivity (defined as $\geq$ 30%), percent of abnormal nuclei harboring the *ATM* deletion, and presence of other key cytogenetic abnormalities including deletion of 17p (17p-), trisomy 12 (+12), 13q-, and Ig heavy chain (IGH) translocation. Treatment and follow-up data were gathered through the database and supplemented with chart review.

Univariate relationships in Cox proportional hazard models at a significance level of $P < .15$ were entered into multivariate modeling. Multivariate analysis was performed using the Cox proportional hazard model with a backwards stepwise selection process to determine predictors of OS and TFS. SPSS software (version 13; SPSS Inc, Chicago, IL) was used for all statistical analyses. A type I error rate of 0.05 was assumed for all statistical tests. This study was approved by the University of BC and BC Cancer Agency clinical research ethics boards.

Results

Between January 2004 and April 2014, 125 CLL patients with 11q- documented at any point during their disease course were identified, of a total of 1044 patients in the database (12%). The median age at diagnosis was 61 years (range, 35-80 years). Sixty-nine patients had 11q- detected before first-line therapy at a median of 0.3 years (range, 0-17 years) from diagnosis; whereas 56 patients had 11q- detected after initiation of therapy. Most patients had more than 1 FISH abnormality, including 14 patients with concomitant 17p-. Characteristics of the overall cohort are shown in Table 1. Twelve patients had documented clonal evolution to 11q- as shown in Table 2. In 9 of the 12, the accumulation of cytogenetic abnormalities occurred after 1 or more treatment courses, including at relapse after allogeneic stem cell transplant in 1 patient. In 3