Increased risk of axial fractures in patients with untreated chronic lymphocytic leukemia: a population-based analysis

Chronic lymphocytic leukemia (CLL) primarily affects older patients, and is frequently characterized by a prolonged asymptomatic phase managed by watchful waiting. Complications of CLL have been described primarily in the context of advanced disease following chemotherapy.[1] By contrast, little is known about its effects on health in the pre-treatment phase. CLL-related bone marrow infiltration is readily identified on spine imaging, and the disease has been linked to altered bone metabolism, resorption, and demineralization.[2-6] We hypothesized that these effects might result in an increased incidence of fractures among older individuals with untreated CLL, which would have clinical implications for prevention strategies in this population.

We conducted a retrospective case-control study using the Surveillance, Epidemiology and End Results registry linked to Medicare claims (SEER-Medicare). We selected CLL cases, aged ≥65 years, diagnosed between 1992 and 2011, as well as controls from a contemporaneous 5% random sample of Medicare beneficiaries without cancer. The SEER-Medicare dataset contains a linkage between files from cancer registries (covering about 28% of the United States population) and billing claims for patients covered by Medicare — a government-sponsored health insurance available to all citizens who are ≥65 years old, disabled, or with end-stage renal disease.[7] Details of the cohort selection are described in the *Online Supplementary Section* (*Online Supplementary Figure S1*). We identified the date of first CLL chemotherapy using codes for related services or specific antineoplastic agents, as previously described in the context of SEER-Medicare analyses (*Online Supplementary Table S1*).[8] Additionally, using data from the 12 months preceding the CLL diagnosis, we ascertained pre-existing osteoporosis, a comorbidity index, and Davidoff's disability status indicator, which is a validated measure of patient's self-reported performance status.[9] Our main endpoint was time to first fracture of the vertebrae or pelvis ("axial" fracture), and fracture of the hip, femur, radius, or ulna ("extremity" fracture), ascertained according to the algorithm by Taylor *et al.*, which is optimized to detect new (incident) fractures.[10] We additionally identified the performance of vertebroplasty or kyphoplasty as a separate confirmatory endpoint.

We matched 16,344 CLL cases to 114,408 controls (ratio 1:7) by date of birth (grouped into 20 strata), sex, race, and reason for Medicare enrollment (age or disability, *Online Supplementary Table S2*). Control subjects were assigned a date of entry identical to the date of CLL diagnosis for the matched case. Time to first fracture was calculated from the date of entry until the date of first chemotherapy, date of death, or date of administrative censoring - whichever was the earliest. We then compared the cause-specific hazard of fractures in proportional hazard Cox models stratified on matched sets. The models additionally included, as variables, the CLL/control status, baseline performance status, osteoporosis, and presence of a prior fracture, and thus report conditional hazard ratios (HR) for incident fracture. The proportional hazard assumption was evaluated using the test by Grambsch and Therneau. We additionally calculated cumulative incidence function (CIF) for fractures, accounting for the competing risks of chemotherapy or intercurrent death. The association of CIF with baseline clinical characteristics was studied using Fine-Gray models. We conducted all analyses using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata/MP 14.1 (StataCorp LP, College Station, TX,USA). Estimates are reported with 95% confidence intervals (CI).

Table 1. Factors associated with the cumulative incidence of axial fractures among patients with untreated chronic lymphocytic leukemia in a multivariable competing risk model.

Factor	Subhazard ratio	95% confidence interval	P
Age at diagnosis			
<70 years	Reference		
70-74 years	1.41	(1.11-1.78)	0.0046
75-79 years	2.07	(1.66-2.58)	<0.0001
80-84 years	2.05	(1.63-2.57)	<0.0001
≥85 years	2.00	(1.58-2.52)	<0.0001
Sex			
Male	Reference		
Female	1.76	(1.55-2.01)	<0.0001
Race/ethnicity			
White	Reference		
Black	0.37	(0.23-0.59)	0.0001
Asian/Other	1.00	(0.56-1.77)	0.99
Poor performance status[a]	0.53	(0.41-0.68)	<0.0001
Prior fracture[a]	2.13	(1.52-2.97)	0.0006
Osteoporosis[a]	1.74	(1.40-2.17)	<0.0001

[a]*Based on Medicare claims from the year preceding the chronic lymphocytic leukemia diagnosis.*

Median age at diagnosis among CLL cases was 77 years. Men constituted 54%, and white patients 94% of the cohort. Poor performance status was identified in 9%, fractures in the year before CLL diagnosis in 1.7%, and osteoporosis in 4.5% of cases. Chemotherapy was initiated for 42% of patients at a median of 6.3 years (CI, 6.0-6.5) from CLL diagnosis. After 5 years from diagnosis, 36% of CLL patients had initiated chemotherapy, 30% died without treatment, and 34% remained alive and without chemotherapy (Figure 1). The median overall survival from CLL diagnosis was 5.2 years (CI, 5.1 to 5.4), significantly shorter than survival among matched healthy controls (9.2 years, CI, 9.1 to 9.2).

During the observed follow-up (54,231 person-years for cases, 718,556 person-years for controls), there were 2,124 incident fractures among CLL cases, and 16,202 among controls. We found a high rate of events coincident with the CLL diagnosis — particularly for extremity fractures, suggesting that the leukemia was discovered during the evaluation of an incidental fracture (*Online Supplementary Figure S2*). The resulting non-proportional hazard was remedied by excluding the first 30 days of observation from analysis.

The conditional hazard of axial fractures among CLL patients was significantly higher compared with controls (HR, 1.37, CI, 1.25-1.50, $P<0.001$), both for vertebral (HR, 1.29, CI, 1.16-1.44, $P<0.001$) and for pelvic fractures (HR, 1.56, CI, 1.33-1.83, $P<0.001$). This excess risk persisted throughout all the years of follow-up. By contrast, we observed no difference for extremity fractures (Figure 2). The hazard of vertebroplasty or kyphoplasty was also increased among CLL cases (HR, 1.35, CI, 1.09-1.67, $P=0.006$). The excess risk of axial fractures among CLL cases compared with controls did not significantly differ by sex (P for interaction=0.18), age ($P=0.82$), race ($P=0.83$), performance status ($P=0.88$) or evidence of prior fracture ($P=0.65$). Among the CLL patients, the

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cumulative incidence of axial fracture after 5 years of watchful waiting was 5.1% (CI, 4.7-5.4), 3.7% for men and 6.7% for women. It progressively increased depending on age at diagnosis, from 2.6% for those <70 years old, to 7.1% for those ≥85 years old. This CIF was significantly higher compared with controls (3.3% overall, P=0.0004, 2.2% for men, and 4.7% for women). In a multivariable model fitted among CLL patients, the cumulative incidence of axial fracture was associated with older age (particularly >75 years), male sex, white race, prior osteoporosis, and prior fracture (Table 1). Conversely, poor performance status was associated with a lower incidence of fracture. Because poor functional status strongly correlated with the competing risk of chemotherapy or death (subhazard ratio, 1.62, CI, 1.53-1.73, P<0.0001, in a corresponding model for competing events), those debilitated patients may have simply not survived long enough to experience CLL-associated fractures.

The fact that the excess risk among CLL patients is specific to axial fractures fits with the concept that interaction of the leukemic infiltrate with its microenvironment may weaken the marrow-rich cancellous bone, but not the cortical bone. Bone metabolism in CLL can be affected by elevated serum levels of tumor necrosis factor α, interleukin 6, interleukin 8, and chemokine (C-C motif) ligand 3 (CCL3),[3-5] expression of the receptor activator of nuclear factor κ-B ligand (RANKL),[6] and vitamin D insufficiency.[11] Our findings constitute the first, to our knowledge, suggestion of a clinically evident, unfavorable effect of untreated CLL on bone health. The lack of association with common trauma-related extremity fractures does not support the alternative mechanistic hypothesis of an increased risk of falls related to weight loss or anemia. We identified clinically significant fractures, for which patients sought medical treatment, as evidenced by an increased rate of procedural interventions. Symptomatic axial fractures are known to impact quality of life, mortality and healthcare costs.[12] For older patients with CLL, the resulting debility may additionally affect their ability to receive future leukemia-directed therapy.

Although many patients live with untreated CLL for years, only a small quantity of rare complications that occur during the "watchful waiting" phase have been recognized, and guidelines are focused on defining indications for chemotherapy or subsequent management, typically summarizing care in the pre-treatment phase as mere "observation". Our study reveals that untreated CLL may have previously unrecognized, unfavorable effects on some aspects of health. With a moderate excess risk of fractures, prospective research is needed to establish whether any screening or primary prevention is warranted for CLL patients undergoing prolonged watchful waiting. Traditional risk factors like age, female sex, white race, or prior osteoporosis, distinguish groups that may derive the highest absolute benefit from potential preventive approaches. However, the risk is equally increased among men, who are currently not offered screening for bone density or any prophylaxis. We should note that Medicare beneficiaries older than 65 years included in our study have shorter survival compared with the overall CLL population. While older patients constitute most CLL cases, our results should be confirmed in a younger or unselected cohort. We could not compare the body mass index, prevalence of smoking, specific comorbidities, serum vitamin D levels, or use of medications (e.g., glucocorticoids); future research using clinical data could establish whether they mediate the increased fracture risk in CLL. It would be of further interest to determine whether measures of leukemic burden like the stage, the extent of marrow infiltration, or molecular abnormalities correlate with the risk of skeletal

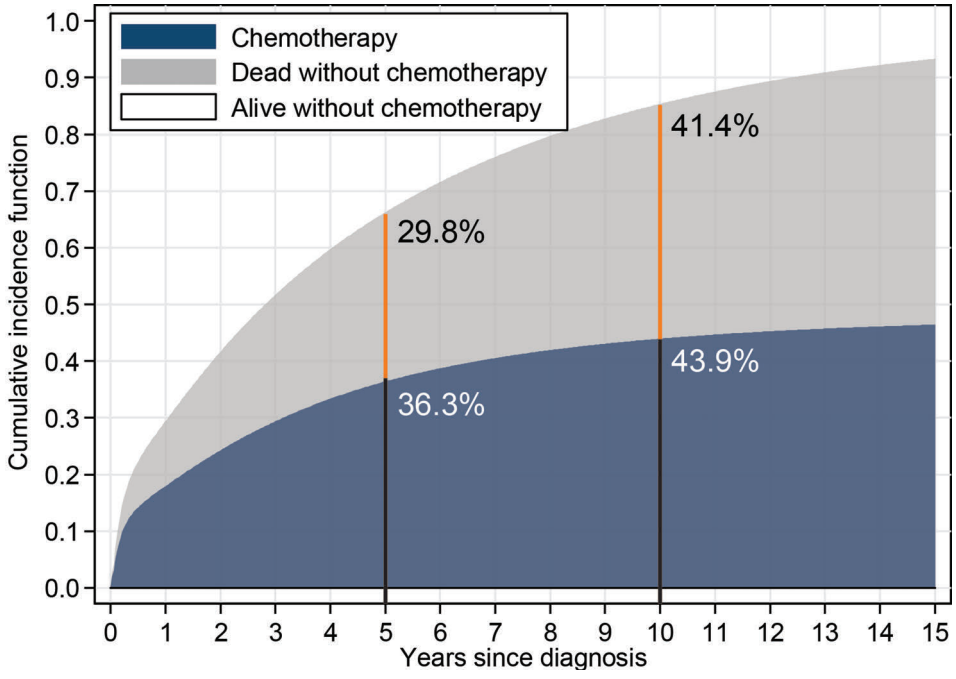

Figure 1. Stacked cumulative incidence curves for initiation of chemotherapy, or death without treatment, among chronic lymphocytic leukemia cases; values of cumulative incidence at 5 and 10 years are listed.

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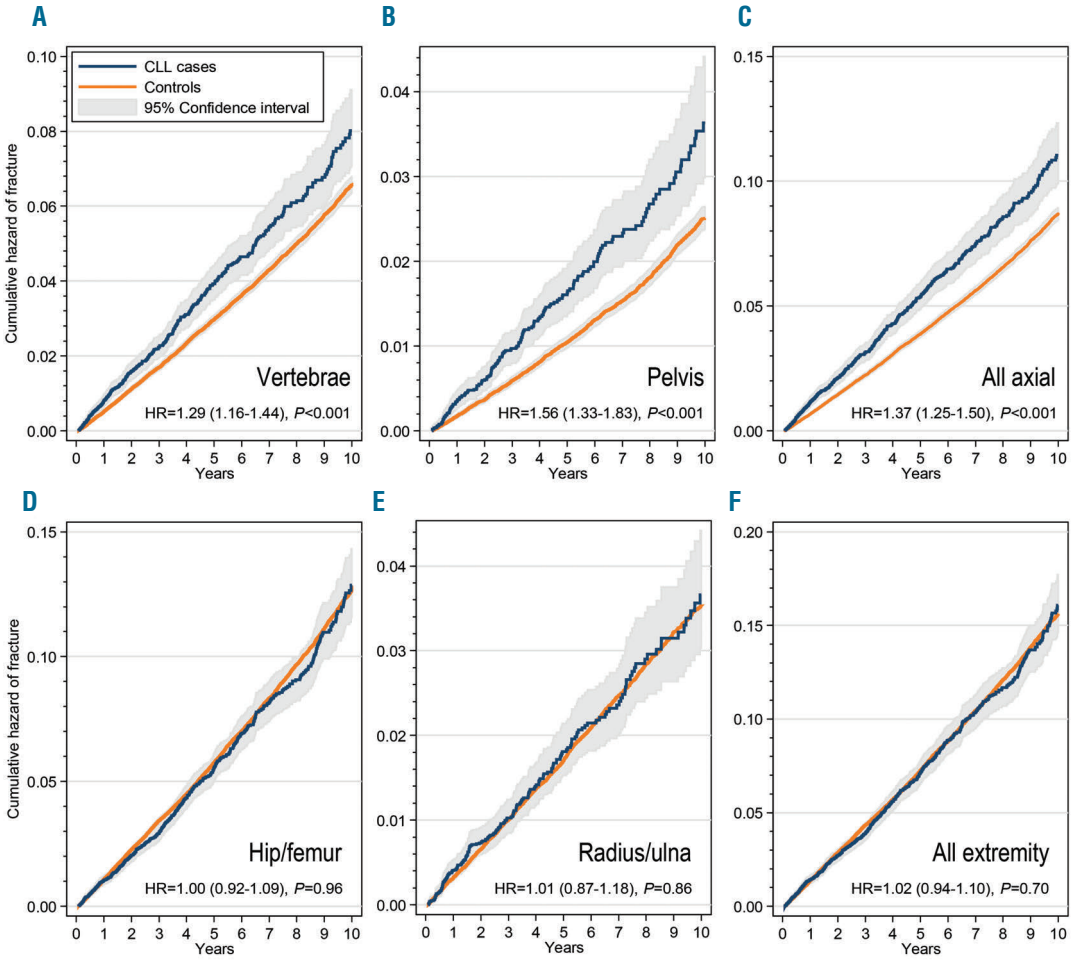

Figure 2. Cumulative hazard of fracture of the vertebrae (A), pelvis (B), all axial fractures (C), hip/femur (D), radius/ulna (E), and all extremity fractures (F), among CLL (chronic lymphocytic leukemia) patients and matched controls. Note the varying scales of the vertical axis on different panels.

morbidity, as they affect the risk of competing events.[13]

The fact that chlorambucil use has been associated with increased bone density in CLL[14] raises a hypothesis that low-intensity, steroid-free chemotherapy might decrease the CLL-induced bone damage. Novel, relatively non-toxic and highly efficacious drugs, like obinutuzumab or ibrutinib, are now available for elderly CLL patients with symptomatic or advanced stage disease, but any potential advantage for patients eligible for watchful waiting remains unknown.[15] However, simple interventions geared towards improving bone health, like weight-bearing exercises and screening for vitamin D insufficiency or osteopenia might prove beneficial for older women and men with CLL. Developing a more active approach to medical care in the pre-treatment phase should be considered as additional clinical evidence emerges.

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doi:10.3324/haematol.2016.148858

Funding: this study was supported by a Medical Research Grant No.20144281 from the Rhode Island Foundation. AJO is partly supported by the American Society of Hematology Research Scholar Award. Presented in part at the 57th American Society of Hematology Annual Meeting & Exposition, December 5-8, 2015, Orlando, FL, USA. This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

Acknowledgments: the authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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