SUPPLEMENTARY APPENDIX

# Chronic lymphocytic leukemia in the elderly: clinico-biological features, outcomes, and proposal of a prognostic model

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***Supplementary data - Online appendix***

## Patients and Methods

*Statistical methods*

The cumulative illness rating scale (CIRS)[1] was retrospectively calculated twice, at the time of chronic lymphocytic leukemia (CLL) diagnosis (CIRS-D) and at the time of frontline therapy (CIRS-T) in those patients requiring intervention. To this purpose, medical records were reviewed and each co-morbid condition was graded as recommended by Salvi et al.[2] Fourteen body systems were evaluated: heart, hypertension, vascular, respiratory, EENT (eye, ear, nose, throat), upper gastrointestinal (GI), lower GI, hepatic, renal, other genital-urinary, muscular-skeletal, neurological, endocrine-metabolic and psychiatric. Each body system was rated from 0 to 4 following these general rules:

0. Absence of disease.
1. Current mild problem or past significant problem.
2. Moderate disability or morbidity requiring first line therapy.
3. Severe problem, significant disability or hard to control chronic problems requiring complex therapeutic regimens.
4. Extremely severe problem, organ failure or severe functional impairment.

CLL was not included in the CIRS, but other malignancies were graded according to the following levels of severity:

1. Cancer diagnosed in the remote past without evidence of recurrence or sequel in the past 10 years or skin cancer excised in the past without major sequel (other than melanoma).
2. No evidence of recurrence or sequel in the past 5 years.
3. Required chemotherapy, radiation, hormonal therapy or surgical procedure for cancer in the past 5 years.
4. Recurrent malignancy or metastasis (other than to lymph glands) or palliative treatment stage.

The CIRS was calculated as the sum of all co-morbid conditions, a number that theoretically ranges from 0 to 56. If a patient had two or more co-morbid conditions in the same body system, only the most severe was graded. The cut-off levels for CIRS-D and CIRS-T that had the greatest discriminative power in terms of overall survival were determined using maximally selected rank statistics (*maxstat* package, R software environment).[3]

Time to first treatment (TTFT) was defined as time from diagnosis to date of initiation of first treatment or last follow-up. For TTFT analysis, CLL-unrelated deaths (i.e. any death before initiation of therapy) were considered as competing events. Cumulative incidence estimates were calculated using the CumIncidence.R function (*cmprsk* package, R) kindly provided by Dr. Scrucca, University of Perugia.[4] Multivariate regression analysis for TTFT also accounted for competing events using the crr-addson function, also provided by Dr. Scrucca.[5]

Overall survival (OS) was defined as the time between diagnosis and the date of death or last follow-up using the Kaplan-Meier method.

When evaluating specifically elderly patients who required therapy a landmark analysis (9 months after treatment) was performed to avoid bias in favor of responders. In the landmark analysis, patients who died or were lost to follow-up before the landmark time were not

evaluated.[6,7] Patients not evaluable and those presenting failure to treatment were grouped together.

Comparisons between different age groups and other covariates were performed by means of the log-rank test. Multivariate analysis of prognostic factors for OS was performed using Cox regression models.

In all multivariate analyses (TTFT and OS), multiple imputation of missing data was implemented using the *Amelia* package (R software environment).[8] Moreover, in all regression models the proportional hazard assumption was tested by plotting Schönfeld residuals against time.

Relative survival and CLL-attributable mortality were calculated using the *relsurv* package (R software environment).[9] Relative survival was defined as the ratio between the observed actuarial survival and the expected survival derived from a subset of the Spanish population matched by age, sex and calendar year of diagnosis, which was obtained from the Human Mortality Database.[10] Several models (additive, multiplicative and transformed) were tested as appropriate and their goodness-of-fit estimated using Brownian bridge statistics.[11]

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