

DR. MASSIMO GENTILE (Orcid ID : 0000-0002-5256-0726)

PROF. LUCA LAURENTI (Orcid ID : 0000-0002-4527-4131)

Article type : Letter to the Editor

Predictive value of the CLL-IPI in CLL patients receiving chemo-immunotherapy as first-line treatment.

Massimo Gentile¹, Tait D Shanafelt², Francesca Romana Mauro³, Gianluigi Reda⁴, Davide Rossi⁵, Luca Laurenti⁶, Maria Ilaria Del Principe⁷, Giovanna Cutrona⁸, Ilaria Angeletti⁹, Marta Coscia¹⁰, Yair Herishanu¹¹, Annalisa Chiarenza¹², Stefano Molica¹³, Stefania Ciolli¹⁴, Neta Goldschmidt¹⁵, Francesco Angrilli¹⁶, Annamaria Giordano¹⁷, Angela Rago¹⁸, Osnat Bairey¹⁹, Giovanni Tripepi²⁰, Kari G Chaffee²¹, Sameer A Parikh²², Ernesto Vigna¹, Katja Zirlik²³, Lev Shvidel²⁴, Idanna Innocenti⁶, Anna Grazia Recchia²⁵, Francesco Di Raimondo¹², Giovanni Del Poeta⁷, Agostino Cortelezzi⁴, Antonino Neri⁴, Manlio Ferrarini²⁶, Gianluca Gaidano²⁷, Neil E Kay², Aaron Polliack¹⁵, Robin Foà³, Fortunato Morabito²⁵

¹UOC Ematologia, Ospedale Annunziata, Cosenza, Italy; ²Department of Medicine, Division of Hematology, Stanford University, CA, United States; ³Ematologia, Università Sapienza, Roma, Italy; ⁴Unità di Ematologia, Fondazione Ca' Granda IRCCS, Ospedale Maggiore Policlinico, Università di Milano, Milan, Italy; ⁵Oncology Institute of Southern Switzerland and Institute of Oncology Research, Bellinzona, Switzerland; ⁶Dipartimento di Ematologia, Università Cattolica "A. Gemelli" Rome, Italy; ⁷Ematologia, Dipartimento di Biomedicina e Prevenzione, Università degli Studi di Roma "Tor Vergata", Rome, Italy; ⁸UOC Patologia Molecolare IRCCS S. Martino-IST, Genova, Italy; ⁹Reparto di Oncoematologia Azienda Ospedaliera Santa Maria di Terni; ¹⁰Divisione di Ematologia, Università di Torino, A.O. Città della Salute e della Scienza di Torino, Italy; ¹¹Department of Hematology, Tel-Aviv Sourasky Medical and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; ¹²Divisione di Ematologia, Università di Catania, Ospedale Ferrarotto, Catania, Italy; ¹³Dipartimento di Onco-ematologia, Azienda Ospedaliera Pugliese-Ciaccio, Catanzaro, Italy; ¹⁴Ematologia Università di Firenze, Florence, Italy; ¹⁵Department of Hematology, Hadassah Medical Center and Faculty of Medicine, Hebrew University, Jerusalem, Israel; ¹⁶Dipartimento di Ematologia, Ospedale Spirito Santo, Pescara, Italy; ¹⁷Ematologia-Azienda Ospedaliero-Universitaria, Policlinico consorziale di Bari, Italy; ¹⁸UOC Ematologia Ospedale Santa Maria Goretti, Latina, Italy; ¹⁹Department of Hematology, Rabin Medical Center, Petah Tikva and Sackler Faculty of Medicine,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ejh.13149

This article is protected by copyright. All rights reserved.

Tel-Aviv University, Tel-Aviv, Israel; ²⁰Consiglio Nazionale delle Ricerche, Istituto di Biomedicina ed Immunologia Molecolare, Reggio Calabria, Italy; ²¹Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA; ²²Department of Internal Medicine, Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA; ²³Department of Haematology and Oncology, University Medical Centre Freiburg, Freiburg, Germany; ²⁴Department of Hematology Kaplan Medical Center, Rehovot and Hadassah Medical Center and Faculty of Medicine, Hebrew University, Jerusalem, Israel; ²⁵Unità di Ricerca Biotecnologica, Azienda Sanitaria Provinciale di Cosenza, Aprigliano (CS), Italy; ²⁶Direzione Scientifica IRCCS, San Martino IST, Genova, Italy; ²⁴Division of Haematology, Department of Translational Medicine, UPO, Novara, Italy.

Correspondence: Massimo Gentile, MD, UOC Ematologia, Azienda Ospedaliera di Cosenza, viale della Repubblica snc, 87100 Cosenza, Italy; e-mail: massim.gentile@tiscali.it; Tel: +39-0984-681329; Fax: +39-0984-681329.

Running title: CLL-IPI predicts PFS after chemo-immunotherapy

Keywords: Chronic lymphocytic leukemia, CLL-IPI, prognosis, chemo-immunotherapy, PFS, Progression-free survival.

To the Editor:

An international collaboration has led to the development of a comprehensive tool [CLL-IPI international prognostic index for CLL] for the predicting of overall survival (OS) in chronic lymphocytic leukemia (CLL).¹ CLL-IPI was based on data collected from 3500 CLL patients and was based on the following parameters: *TP53* deletion and/or mutation, *IGHV* mutational status, β 2-microglobulin plasma levels, clinical stage, and age. CLL-IPI provides the means to stratify CLL patients in the daily clinical practice (Supplementary Table 1).¹ Although validated for OS²⁻⁴ and time to first treatment (TTFT),⁵ the predictive value of CLL-IPI on progression-free survival (PFS) has until now only been demonstrated in a single study on patients treated with chlorambucil (CLB), as monotherapy, or in combination with obinutuzumab or rituximab, as a first-line approach (CLL11 study),⁶ and presented as a poster at the annual meeting of the American Society of Hematology (ASH) in 2016.

The aim of the present study was to assess the predictive value of the CLL-IPI, determined at the time of first treatment, for PFS in a cohort of patients with CLL who underwent different front-line chemo-immunotherapy treatment regimens: fludarabine-cyclophosphamide-rituximab (FCR), bendamustine-rituximab (BR), pentostatin-cyclophosphamide-rituximab (PCR) or pentostatin-cyclophosphamide-ofatumumab (PCO).

This collaborative study included CLL patients from Italian, American, Israeli and German centers, who had received one of the above front-line regimens and for whom all five CLL-IPI markers had been evaluated at the time of first treatment. PFS was estimated for low-, intermediate-, high-, and very high-risk CLL-IPI scores. Additionally, risk-specific OS was also assessed. Methods included Kaplan-Meier curve, log-rank test, and Cox regression analyses. The prognostic accuracy of the predictive model was assessed by the Harrell C index (further details are in the Supplemental Appendix).

A total of 845 CLL patients were included in this analysis and the majority were Binet stage B and C (77.9%). The median age was 63 years and 566 (67%) were male. Baseline clinical features are listed in Table 1; 402 cases received FCR, 252 BR, 142 PCR and 49 PCO between January 2003 and September 2016. After a median follow-up of 3.7 years from therapy start (range, 3 months to 15.7 years), 157 patients had died and 402 experienced an event (death or progression). All clinicians applied IWCLL criteria to start therapy and to assess CLL progression. All patients were followed every 3 months.⁷

First, we evaluated the capability of the CLL-IPI score to predict PFS. Due to missing data related to *TP53* mutations, del17p was used as the sole marker of *TP53* status. All selected markers had an independent prognostic impact on PFS (Supplementary Table 2).

According to the CLL-IPI score, 183 patients (21.7%) were low-risk, 337 (39.9%) intermediate-risk, 276 (32.7%) high-risk, and 49 (5.8%) very high-risk.

PFS differed between the various CLL-IPI risk groups studied. The 3-year PFS probability was 82.6% (HR=1) for low-risk, 63.6% (HR=2.27; 95%CI 1.65–3.12, P<0.0001) for intermediate-risk, 53.9% (HR=2.87, 95%CI 2.08–3.97, P<0.0001) for high-risk, and 32.8% (HR=5.01, 95%CI 3.29–7.64, P<0.0001) for very high-risk patients (Figure 1A). The C-statistic for PFS was 0.61 (P<0.001).

These results demonstrate the predictive power of CLL-IPI, determined at the time of first treatment, on PFS of CLL patients receiving different chemo-immunotherapy regimens as first-line treatment. Our data are in line with those of Goede et al⁶ who reported that groups with different PFS could be distinguished in a cohort of elderly unfit CLL patients receiving CLB or CLB plus an anti-CD20 antibody as first-line treatment (CLL11 trial), based upon the CLL-IPI criteria. These findings are also

consistent with the observation that *TP53* disruption, *IGHV* unmutated status or $\beta 2M$ levels, when considered as single parameters, are also associated with treatment outcomes after chemo-immunotherapy.⁸⁻¹⁴

Moreover, when the CLL-IPI was forced in a multivariate model together with the chemo-immunotherapy regimen (FCR/PCR/PCO vs BR), both parameters remained significantly associated with PFS (CLL-IPI, HR 1.58; 95%CI 1.41-1.77, $P < 0.0001$; FCR-PCR-PCO vs BR, HR 1.31; 95% CI 1.02-1.67, $P = 0.033$), showing that the CLL-IPI score allows of predicting the risk of progression regardless of the different chemo-immunotherapy approach.

Stratification of patients according to the CLL-IPI criteria, evaluated at the time of first-line treatment, predicted significant differences also in terms of OS. Thus, low-risk patients had a 3-year OS probability of 96.6% (HR=1), intermediate-risk 92.8% (HR=3.73, 95%CI 1.84–7.57, $P < 0.0001$), high-risk 81.4% (HR=7.35, 95%CI 3.66–14.77, $P < 0.0001$), and very high-risk 64.7% (HR=17.3, 95%CI 8.01–37.27, $P < 0.0001$) (Figure 1B). The Harrell C-statistic was 0.69 ($P < 0.001$) for predicting OS.

Our data confirm the prognostic power of CLL-IPI when evaluated at the time of first-line therapy in patients treated with more aggressive chemo-immunotherapy regimens. These findings are in keeping and extend those reported in the original paper¹ and by Goede et al.⁶ Overall, these results clearly indicate that CLL-IPI predicts PFS and OS independently of the type of chemo-immunotherapy administered.

In conclusion, this is a validation study for CLL-IPI, assessed at the time of first-line treatment, in CLL patients who received a variety of chemo-immunotherapy approaches. The results confirm the ability of CLL-IPI to stratify patients' outcomes in terms of both PFS and OS.

Contributions: M.G., F.R.M., F.M., T.D.S., A.P., R.F., A.N., G.G., F.F., N.E. K., and M.F. designed the study, analyzed and interpreted data, and wrote the manuscript; M.G., G.T., K.G.C., and F.M. performed statistical analysis; G.C., A.G.R., A.N., F.F., and M.F. performed central laboratory tests; G.R., D.R., L.L., M.I.D.P., I.A., M.C., Y.H., A.C., S.M., S.C., N.G., F.A., A.G., A.R., O.B., S.A.P., E.V., K.Z., L.S., I.I., F.D.R., G.D.P., and A. Cortelezzi included patients and collected clinical data; all authors gave their final approval for the manuscript.

Conflict-of-interest disclosure: The authors declare no competing interests.

References

1. CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. International CLL-IPI working group. *Lancet Oncol.* 2016; 17: 779-90.
2. da Cunha-Bang C, Christiansen I, Niemann CU. The CLL-IPI applied in a population-based cohort. *Blood.* 2016; 128: 2181-2183.
3. Gentile M, Shanafelt TD, Rossi D, Laurenti L, Mauro FR, Molica S, et al. Validation of the CLL-IPI and comparison with the MDACC prognostic index in newly diagnosed patients. *Blood.* 2016; 128: 2093-2095.
4. Gentile M, Shanafelt TD, Mauro FR, Laurenti L, Rossi D, Molica S, et al. Comparison between the CLL-IPI and the Barcelona-Brno prognostic model: Analysis of 1299 newly diagnosed cases. *Am J Hematol.* 2018; 93: E35-E37.
5. Molica S, Shanafelt TD, Giannarelli D, Gentile M, Mirabelli R, Cutrona G, et al. The chronic lymphocytic leukemia international prognostic index predicts time to first treatment in early CLL: Independent validation in a prospective cohort of early stage patients. *Am J Hematol.* 2016; 91: 1090-1095.
6. Goede V, Bahlo J, Kutsch N, Fischer K, Fink AM, Fingerle-Rowson G, et al. Evaluation of the International prognostic index for chronic lymphocytic leukemia (CLL-IPI) in elderly patients with comorbidities: analysis of the CLL11 study population. *Blood.* 2016; 128 (suppl 1): abstract 4401.
7. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: A report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood.* 2008; 111: 5446–5456.
8. Tam CS, O'Brien S, Wierda W, Kantarjian H, Wen S, Do KA, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood.* 2008; 112: 975-80.
9. Rossi D, Terzi-di-Bergamo L, De Paoli L, Cerri M, Ghilardi G, Chiarenza A, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. *Blood.* 2015; 126: 1921-4.
10. Fischer K, Bahlo J, Fink AM, Goede V, Herling CD, Cramer P, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood.* 2016; 127: 208-15.
11. Gentile M, Shanafelt TD, Reda G, Mauro FR, Zirlik K, Ciolli S, et al. Validation of a biological score to predict response in chronic lymphocytic leukemia patients treated front-line with bendamustine and rituximab. *Leukemia.* 2018 Mar 20. doi: 10.1038/s41375-018-0100-6.

12. Gentile M, Zirlik K, Ciolli S, Mauro FR, Di Renzo N, Mastrullo L, et al. Combination of bendamustine and rituximab as front-line therapy for patients with chronic lymphocytic leukaemia: multicenter, retrospective clinical practice experience with 279 cases outside of controlled clinical trials. *Eur J Cancer*. 2016; 60: 154-65.
13. Eichhorst B, Fink AM, Bahlo J, Busch R, Kovacs G, Maurer C, et al; international group of investigators; German CLL Study Group (GCLLSG). First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016; 17: 928-942.
14. Fischer K, Cramer P, Busch R, Böttcher S, Bahlo J, Schubert J, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol*. 2012; 30: 3209-16.

Figure Legends

Figure 1. Progression-free survival (A) and overall survival (B) of the entire CLL cohort according to CLL-IPI score.

Table 1. Clinical features

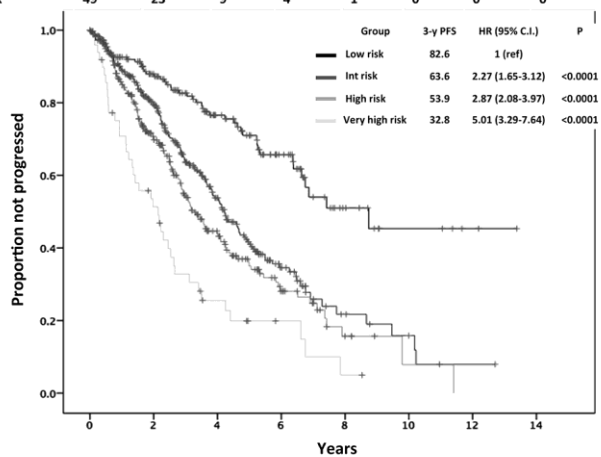
Features	All cases (N=845)
	No (%)
Age, years	
≤65	506 (59.9)
>65	339 (40.1)
Sex	
Male	566 (67)
Female	279 (33)
Binet stage	
A	187 (22.1)
B	504 (59.6)
C	154 (18.2)
β2-M (mg/L)	
≤3.5	543 (64.3)
>3.5	302 (55.7)
IGHV mutational status	
mutated	329 (38.9)
unmutated	516 (61.1)
17p deletion	
no	791 (93.6)
yes	54 (6.4)
CLL-IPI score	
low	183 (21.7)
intermediate	337 (39.9)
high	276 (32.7)
very high	49 (5.8)
Therapy	

FCR	402 (47.6)
BR	252 (29.8)
PCR	142 (16.8)
PCO	49 (5.8)

A

No. of pts at risk

Low risk	183	122	75	38	12	5	2	0
Int risk	336	214	100	32	9	4	1	0
High risk	276	148	60	21	5	1	0	0
Very high risk	49	23	9	4	1	0	0	0



B

No. of pts at risk

Low risk	183	139	99	57	24	11	5	0	0
Int risk	336	252	162	77	34	15	8	2	0
High risk	276	191	107	45	21	3	2	1	0
Very high risk	49	29	16	7	3	0	0	0	0

