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

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

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

Massimo Gentile[1], Tait D Shanafelt[2], Francesca Romana Mauro[3], Gianluigi Reda[4], Davide Rossi[5], Luca Laurenti[6], Maria Ilaria Del Principe[7], Giovanna Cutrona[8], Ilaria Angeletti[9], Marta Coscia[10], Yair Herishanu[11], Annalisa Chiarenza[12], Stefano Molica[13], Stefania Ciolli[14], Neta Goldschmidt[15], Francesco Angrilli[16], Annamaria Giordano[17], Angela Rago[18], Osnat Bairey[19], Giovanni Tripepi[20], Kari G Chaffee[21], Sameer A Parikh[22], Ernesto Vigna[1], Katja Zirlik[23], Lev Shvidel[24], Idanna Innocenti[6], Anna Grazia Recchia[25], Francesco Di Raimondo[12], Giovanni Del Poeta[7], Agostino Cortelezzi[4], Antonino Neri[4], Manlio Ferrarini[26], Gianluca Gaidano[27], Neil E Kay[2], Aaron Polliack[15], Robin Foà[3], Fortunato Morabito[25]

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

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

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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, β2-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 OS[2-4] 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 al[6] 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 β2M 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 paper[1] 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.

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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)