TO THE EDITOR:

Relative dose intensity of obinutuzumab-chlorambucil in chronic lymphocytic leukemia: a multicenter Italian study

Alberto Fresa,1,2 Francesco Autore,2 Alfonso Piciocchi,3 Gioacchino Catania,4 Andrea Visentin,5 Annamaria Tomasso,1 Marina Moretti,6 Candida Vitale,7,8 Annalisa Chiarenza,9 Francesca Morelli,10 Paolo Sportoletti,11 Roberto Marasca,12 Giuseppe Sapienza,13 Annarosa Cuccaro,14 Roberta Murru,15 Alessandro Sanna,16 Caterina Patti,13 Ilaria Angeletti,6 Marta Coscia,7,8 Livio Trentin,5 Daniela Pietrasanta,4 Idanna Innocenti,2 and Luca Laurenti1,2

1Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Rome, Italy; 2Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; 3Gruppo Italiano Malattie EMatologiche dell’Adulto (GIMEMA) Foundation, Rome, Italy; 4Division of Hematology, Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; 5Hematology and Clinical Immunology Unit, Department of Medicine, University of Padua, Padua, Italy; 6Reparto di Oncoematologia Azienda Ospedaliera Santa Maria di Terni, Terni, Italy; 7University Division of Hematology, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; 8Department of Molecular Biotechnology and Health Sciences, University of Turin, Turin, Italy; 9Division of Hematology, Policlinico, Department of Surgery and Medical Specialties, University of Catania, Catania, Italy; 10Department of Hematology, Università degli Studi di Firenze, Florence, Italy; 11Centro di Ricerca Emato-Oncologica (CREO), University of Perugia, Perugia, Italy; 12Hematology Unit, Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy; 13Division of Oncohematology, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy; 14Hematology Unit, Center for Translational Medicine, Azienda USL Toscana NordOvest, Livorno, Italy; 15Hematology and Stem Cell Transplantation Unit, Ospedale A. Businco, Cagliari, Italy; and 16Department of Hematology, Azienda Ospedaliera-Universitaria Careggi, Florence, Italy

Obinutuzumab (G) in combination with chlorambucil (Chl) has been approved in Italy in 2017 as frontline treatment for patients with chronic lymphocytic leukemia (CLL) and comorbidities, following results of the CLL11 trial1 and real-life studies.2-4 Few studies have focused on reduction of relative dose intensity (RDI) in CLL.5,6 The aim of this study was to evaluate the impact of reduced RDI of G-Chl on the overall response rate (ORR), progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS); we also wanted to identify patients at higher risk for dose reductions. We collected and retrospectively analyzed data of 130 patients diagnosed with CLL and comorbidities from the Italian centers with the highest use of the G-Chl regimen outside clinical trials between 2017 and 2020. Patients’ characteristics are shown in supplemental Table 1. The study was conducted according to the Helsinki Declaration, Good Clinical Practice, and the applicable national regulations; all patients provided written informed consent, and the study was approved by the Institutional Ethical Committee of the Fondazione Policlinico Agostino Gemelli IRCCS. The RDI was calculated as the ratio between the dose actually delivered over time and the expected correct dose: a dose reduction of 20% was considered the best cutoff according to previous studies4,5 and was confirmed by a receiver-operating characteristic analysis in this study. For each patient, data were collected from the medical records of each center in order to assess clinical and laboratory characteristics, focusing in particular on the different categories of comorbidities. Specifically, we investigated the impact on RDI of each parameter of the cumulative illness rating scale (CIRS) taken individually and also the impact of CIRS >6, CIRS >8, or CIRS with at least 1 component with grading ≥3 (CIRS 3+).

The median age was 76 years (range, 42-88); 91% of patients were over 65 years. The median CIRS score was 7 (range, 1-18), 72% of patients had a creatinine clearance <70 mL/min, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) was ≥2 in 28% of patients. The median follow-up was 29.1 months (range, 1.8-55.7). Overall, the ORR was 88% (26% clinical complete response, 62% partial response), median PFS was 33 months, median TTNT was 40 months, and 24-month and 36-month OS were 88% and 85%, respectively (Figure 1). Collectively, these findings are aligned with those reported in the literature.1-3 In multivariate analysis, the only factor that was associated with OS was CIRS ≥3.
More than half of the patients (58.5%) received the standard G-Chl regimen without change in dose of either obinutuzumab or chlorambucil. Reduction of obinutuzumab dose occurred in 24% (n = 31) of patients; a reduction of >20% occurred in 19% (n = 20); chlorambucil dose was reduced in 32% (n = 42) of patients. Although dose modifications of chlorambucil did not have an impact, a decrease of >20% of RDI in obinutuzumab negatively impacted outcome in terms of ORR, PFS, and TTNT but not OS (Figure 1). ORR was significantly lower in the group with an RDI reduction of >20% (93% vs 61%, P = .001). We then compared the median PFS and TTNT in patients who did or did not receive a reduced RDI >20% (Table 1); there was a significant decrease in both PFS and TTNT in patients with a reduced RDI of >20% (PFS 17.2 vs 37.3 months; TTNT 24.4 months vs NR, respectively; P = .001). The difference was maintained at 2 and 3 years (Table 1), even when considering the subgroup with 1% to 20% reduction (supplemental Figures 1-3).

Considering the causes of dose reduction, ≤20% reduction was due to 2 infusion-related reactions (RRRs), grade 1 to 2; 6 hematologic toxicities; and 3 extrahematologic toxicities. Patients who reduced >20% experienced: 4 RRs, grade 3 to 4; 1 RRR, grade 1 to 2; 10 extrahematologic toxicities (5 infections in neutropenic patients, 2 atrial fibrillation, 1 acute renal failure, 1 transaminitis, and 1 gastrointestinal toxicity); and 5 hematologic toxicities (all grade 3-4). In no patient was the administered dose of obinutuzumab reduced per se; overall dose reduction was due to missed doses or treatment discontinuation.

We then looked at factors predicting obinutuzumab dose reduction, and we found 2 significant predictors: a lower absolute neutrophil count at the start of treatment (P = .018) and an ECOG performance status ≥2 (P = .027). Notably, neither neutropenia nor ECOG showed an impact on OS, PFS, and TTNT per se (supplemental Tables 7 and 9), confirming the impact of G-reduction on survivals.

Dose modification of chlorambucil was linked to a higher comorbidity burden, expressed both as CIRS >8 (43% vs 25%, P = .045) and CIRS 3+ (67% vs 45%, P = .026).

To date, only 1 study, conducted by European Research Initiative on CLL and the Israeli group, has reported the impact on outcome of RDI G-Chl. They showed an impact on PFS and OS of any obinutuzumab dose reduction.3 Our choice to evaluate the impact of a 20% RDI reduction is based on 2 main considerations: first, previous studies on CLL have evaluated a reduction in chemotherapy with a 20% cutoff based on the clinical need to tailor dosing on patient tolerability.5,6 Second, obinutuzumab is associated with side effects (e.g., RR,1,6 nonovert disseminated intravascular coagulopathy with thrombocytopenia,7 prolonged neutropenia, etc.), which frequently causes delayed or missed administration of obinutuzumab, especially on the second and/or eighth day of the

Figure 1. Outcome of the treatment chlorambucil-obinutuzumab. (A) PFS, TTNT, and OS curves of the entire cohort. (B) PFS, TTNT, and OS curves by change in dose of chlorambucil. (C) PFS, TTNT, and OS curves by obinutuzumab RDI reduction >20%.
first course. As a result, patients on treatment often skip at least 1 dose. This study suggests that patients treated with at least 80% RDI achieve comparable response and survival when compared with patients given the full dose of obinutuzumab. Of note is the fact that, despite G-Chl having one of the lowest doses among several possible chlorambucil regimens, the reduction in chlorambucil is not associated with adverse prognosis, confirming the greater significance of obinutuzumab RDI in outcome.

The impact of the performance status in CLL patients has been investigated in several studies, mostly for chemoimmunotherapy studies which showed a negative impact of ECOG PS on outcome, considering that our cohort includes exclusively unfrail patients, almost all of whom are older than 65 years.

In conclusion, a decrease >20% of obinutuzumab RDI results in a worse outcome in terms of ORR, PFS, and TTNT; a smaller dose reduction (≤20%), in contrast, showed no difference when compared with 100% RDI. ECOG PS ≥2 could be considered a predictor of dose reduction, although it does not affect prognosis per se. On the other hand, the need for multiple dose reductions in unfrail patients should prompt reevaluation of performance status as well; frail patients may have a worse outcome if treatment is not optimized. These results need further investigation in the coming years, when obinutuzumab will be increasingly used in combination with venetoclax, to see if the survival impact of RDI reduction could be overcome by a more effective oral agent.

Acknowledgments: This work was supported by a grant for secondary data use from Roche S.p.A.

Contribution: F.A., G.C., A.V., A.T., M.M., C.V., A.Chiarenza, F.M., P.S., R.M., G.S., A. Cuccaro, R.M., A.S., C.P., I.A., M.C., L.T., D.P., P.S., R.M., G.S., A. Cuccaro, R.M., A.S., C.P., I.A., M.C., L.T., D.P., and I.I. provided the data; A.P. performed the statistical analysis; F.A. and L.L. wrote the manuscript; and L.L. supervised the project.

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

ORCID profiles: F.A., 0000-0002-7868-7469; G.C., 0000-0002-1743-9525; A.V., 0000-0003-2071-7200; M.M., 0000-0003-1161-9995; C.V., 0000-0002-2592-8724; P.S., 0000-0002-5630-9862; R.M., 0000-0002-6431-6878; G.S., 0000-0002-0149-0764; A.C., 0000-0002-0237-1839; L.T., 0000-0003-1222-6149; I.I., 0000-0001-7290-260X; L.L., 0000-0002-8327-1396.

Correspondence: Luca Laurenti, Fondazione Policlinico Universitario A. Gemelli IRCCS, Istituto di Ematologia, Largo A. Gemelli 8, 00168 Rome, Italy; e-mail: luca.laurenti@unicatt.it.

References

1. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014;370(12):1101-1110.
2. Długosz-Danecka M, Jurczak W,Łatka-Cabala E, et al. Efficacy and safety of the obinutuzumab-chlorambucil combination in the frontline treatment of patients with chronic lymphocytic leukemia: results of a phase IV trial. Leukemia. 2018;32(6):1435-1440.
treatment of elderly CLL patients with comorbidities – Polish Adult Leukemia Group (PALG) real-life analysis. *Pol Arch Intern Med.* 2018;128(7-8):421-426.

3. Herishanu Y, Shaulov A, Fineman R, et al. Frontline treatment with the combination obinutuzumab + chlorambucil for chronic lymphocytic leukemia outside clinical trials: Results of a multinational, multicenter study by ERIC and the Israeli CLL study group. *Am J Hematol.* 2020;95(6):604-611.

4. Panovská A, Němcová L, Někvindová L, et al. Real-world data on efficacy and safety of obinutuzumab plus chlorambucil, rituximab plus chlorambucil, and rituximab plus bendamustine in the frontline treatment of chronic lymphocytic leukemia: the GO-CLLEAR Study by the Czech CLL Study Group. *Hematol Oncol.* 2020;38(4):509-516.

5. Bouvet E, Borel C, Obéric L, et al. Impact of dose intensity on outcome of fludarabine, cyclophosphamide, and rituximab regimen given in the first-line therapy for chronic lymphocytic leukemia. *Haematologica.* 2013;98(1):65-70.

6. Gentile M, Zirlik K, Ciolli S, et al. Combination of bendamustine and rituximab as front-line therapy for patients with chronic lymphocytic leukemia: multicenter, retrospective clinical practice experience with 279 cases outside of controlled clinical trials. *Eur J Cancer.* 2016;60:154-165.

7. Fresca A, Autore F, Innocenti I, et al. Non-overt disseminated intravascular coagulopathy associated with the first obinutuzumab administration in patients with chronic lymphocytic leukemia. *Hematol Oncol.* 2021;39(3):423-427.

8. Manda S, James S, Wang R, Krishnan R, Danilov AV. Impact of comorbidities on treatment outcomes in chronic lymphocytic leukemia: a retrospective analysis. *Blood.* 2014;124(21):1912.

9. Strugov V, Stadnik E, Virts Y, Andreeva T, Zaritskey A. Impact of age and comorbidities on the efficacy of FC and FCR regimens in chronic lymphocytic leukemia. *Ann Hematol.* 2018;97(11):2153-2161.

10. Mattsson A, Sylvan SE, Asklid A, et al. Risk-adapted bendamustine + rituximab is a tolerable treatment alternative for elderly patients with chronic lymphocytic leukemia: a regional real-world report on 141 consecutive Swedish patients. *Br J Haematol.* 2020;191(3):426-432.

11. Laurenti L, Innocenti I, Autore F, et al. Chlorambucil plus rituximab as front-line therapy for elderly and/or unfit chronic lymphocytic leukemia patients: correlation with biologically-based risk stratification. *Haematologica.* 2017;102(9):e352-e355.

12. Autore F, Innocenti I, Corrente F, et al. Front-line therapy for elderly chronic lymphocytic leukemia patients: bendamustine plus rituximab or chlorambucil plus rituximab? Real-life retrospective multicenter study in the Lazio region. *Front Oncol.* 2020;10:848.

13. Gordon MJ, Chermetski M, Alqhahtani H, et al. Comorbidities predict inferior outcomes in chronic lymphocytic leukemia treated with ibrutinib. *Cancer.* 2018;124(15):3192-3200.

14. Cuneo A, Mato AR, Rigolin GM, et al; GIMEMA, European Research Initiative (ERIC) on CLL, US study group. Efficacy of bendamustine and rituximab in unfit patients with previously untreated chronic lymphocytic leukemia. Indirect comparison with ibrutinib in a real-world setting. A GIMEMA-ERIC and US study. *Cancer Med.* 2020;9(22):8468-8479.

15. Tedeschi A, Frustaci AM, Mauro FR, et al. Do age, fitness and concomitant medications influence management and outcomes of CLL patients treated with ibrutinib? *Blood Adv.* 2021;5(24):5490-5500.

16. Fresca A, Autore F, Galli E, et al. Treatment options for elderly/unfit patients with chronic lymphocytic leukemia in the era of targeted drugs: a comprehensive review. *J Clin Med.* 2021;10(21):5104.

17. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med.* 2019;380(23):2225-2236.

18. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2020;21(9):1188-1200.