Tyrosine kinase inhibitor discontinuation in non-allografted Philadelphia-positive acute lymphoblastic leukemia patients: a Campus ALL real-life study

Philadelphia-positive acute lymphoblastic leukemia (Ph^+ ALL) patients are currently treated with tyrosine kinase inhibitors (TKI) in combination with either steroids, chemotherapy or, more recently, immunotherapy. In the past, allogeneic stem cell transplant (SCT) was considered the only potential curative option. With the introduction of more potent TKI, as well as immunotherapy, particularly blinatumomab, the role of SCT is nowadays debated, particularly for patients who achieve an early molecular response.[1-3]

Patients not undergoing SCT will receive TKI indefinitely even though long-term TKI administration may be associated with serious side effects (including off-target toxicities such as vascular events, cytopenias, and hepatotoxicity), have a high economic burden, and can, in some cases, negatively impact on patients' quality of life.

TKI discontinuation has proven feasible in chronic myeloid leukemia (CML) and is now a reality in the clinical management of CML patients with well-defined biological features.[4,5]

In view of the efficacy of the novel approaches combining a TKI with immunotherapy with long-term survival rates approaching 80%,[2] it is becoming of primary interest to investigate if TKI discontinuation may become a reality also for Ph^+ ALL and, should this be the case, for which patients. To this end, we collected and hereby report the outcome of a series of adult Ph^+ ALL patients in complete hematologic response who did not undergo a SCT and discontinued TKI treatment for any reason different from relapse/progression. The study was approved by local ethic committee (CE 5629, 21/11/2019).

Retrospective clinical data on 18 patients treated at eight hematology centers participating in the Campus ALL network in Italy were collected. Their frontline treatment included a TKI with or without mild chemotherapy according to the center policy and/or to the ongoing national clinical trial. For the purpose of this study, only patients who were treated with a chemotherapy-free approach or with the addition of low-intensity chemotherapy were considered. Major molecular response (MMR) was defined as a level of *BCR::ABL1/ABL1* of <0.01%. Molecular relapse was defined as the loss of MMR in two consecutive samples. Overall survival (OS) was calculated from the time of TKI discontinuation to the last follow-up. Treatment-free remission (TFR) was defined as the time interval between the date of therapy discontinuation and the date of TKI resumption due to molecular/hematologic relapse or, if this did not occur, the date of the last follow-up. Relapse-free survival (RFS) was calculated from the time of TKI discontinuation to the last follow-up or to the date of molecular/hematologic relapse. Median follow-up was estimated using the reverse Kaplan-Meier method.

The median age of our cohort was 65 years (range, 22-84); eight patients (44.4%) were females, 11 harbored a p190 transcript and seven a p210 transcript. Conventional karyotyping at diagnosis showed the t(9;22) translocation as the only cytogenetical abnormality in nine patients. In two paitients, the t(9;22) translocation was found in the context of a complex karyotype. One additional patient had a del(11) in addition to the t(9;22) translocation and another one had a normal karyotype. Karyotyping failed in five patients.

The first TKI administered in this cohort was imatinib in nine patients (50%), dasatinib in four (22%), sequential nilotinib/imatinib (GIMEMA LAL1408[6]) in one (6%) and ponatinib in four (22%). During the follow-up, six patients were maintained on the same TKI since the start of treatment. The median number of TKI used was two (range, 1-3). The median time of TKI exposure prior to discontinuation was 84.5 months (range, 4-205). At the time of discontinuation, 17 of 18 patients were in complete molecular response. The median time to molecular response achievement was 5 months (range, 1-69). This information was not available for one patient. The characteristics of patients are summarized in Table 1.

The reason for not undergoing a SCT was a clinical decision (mainly due to age/unfitness and sustained molecular response) in 12 patients, donor unavailability in three and patient's refusal in the remaining three.

The main reason leading to TKI discontinuation was toxicity in 12 patients and clinical or patient's decision in the other six patients. Reported toxicities were vascular or cardiac events (N=7), recurrent pleural effusion (N=2), severe skin ulcerations (N=1), severe diffuse muscle cramps and severe gastrointestinal symptoms (N=1).

The median time of TFR after discontinuation was 14 months (range, 1-96). At the last follow-up, five of the 18 patients (28%) experienced a molecular relapse after a median time of 4 months from TKI discontinuation. Four of the five patients restarted treatment with the last TKI administered and regained a molecular remission; three of five patients are alive and well at the last follow-up after

Table 1. Patients' characteristics.

	Sex	Transcript	1° TKI used	Last TKI	Reason for discontinuation	MRD at TKI stop	Time on treatment in months	Time to CMR in months	Time from stop TKI in months	TFR status	Status at last FU	Time from TKI restart in months
P1	M	p190	Ponatinib	Ponatinib	Toxicity	Molecular response	98	5	8	Remission	Alive in CR	-
P2	M	p210	Ponatinib	Ponatinib	Toxicity	NA	93	39	3	Molecular relapse	Alive in CR	-
P3	F	p190	Dasatinib	Ponatinib	Toxicity	Molecular response	66	18	10	Remission	Alive in CR	-
P4	F	p190	Ponatinib	Ponatinib	Toxicity	Molecular response	39	1	46	Remission	Alive in CR	-
P5	M	p210	Imatinib	Ponatinib	P decision	Molecular response	94	20	7	Remission	Alive in CR	-
P6	F	p190	Dasatinib	Imatinib	Toxicity	Molecular response	76	5	50	Remission	Alive in CR	-
P7	F	p190	Ponatinib	Ponatinib	Toxicity	Molecular response	35	1	50	Remission	Dead (for other cause)	-
P8	M	p190	Dasatinib	Dasatinib	P decision	Molecular response	113	52	10	Remission	Alive in CR	-
P9	F	p190	Imatinib	Imatinib	P decision	Molecular response	205	73	2	Molecular relapse	Alive in CR	5
P10	M	p190	Imatinib	Imatinib	Toxicity	Molecular response	73	1	5	Remission	Alive in CR	-
P11	M	p210	Imatinib	Nilotinib	P decision	Molecular response	115	8	31	Remission	Alive in CR	-
P12	F	P210	Imatinib	Imatinib	P decision	Molecular response	145	3	96	Remission	Alive in CR	-
P13	M	p190	Imatinib	Imatinib	Toxicity	Molecular response	160	1	38	Remission	Alive in CR	-
P14	F	p210	Nilotinib/ Imatinib	Nilotinib/ Imatinib	Toxicity	Molecular response	38	5	31	Molecular relapse	Dead (for other cause)	39
P15	M	p210	Imatinib	Imatinib	Toxicity	Molecular response	134	4	14	Molecular relapse	Alive in CR	48
P16	M	p190	Imatinib	Dasatinib	Toxicity	Molecular response	4	5	1	Remission	Dead (for unknown cause)	-
P17	M	p190	Dasatinib	Dasatinib	Toxicity	Molecular response	56	37	14	Remission	Alive in CR	-
P18	M	p190	Imatinib	Dasatinib	P decision	Molecular response	31	16	4	Molecular relapse	Alive in CR	136

TKI: tyrosine kinase inhibitors; MRD: minimal residual disease; CMR: complete molecular response; CR: complete response; TFR: treatment-free remission; FU: follow-up; F: female; M: male; P: patient; NA: not available.

5, 48, and 136 months, respectively. One patient ultimately died from a metastatic gastric cancer after 39 months from TKI restart (Table 1; Figure 2). The last patient refused to restart treatment and is being closely monitored by molecular analysis. At the last follow-up (March 2024) *BCR::ABL1/ABL1* was 0.83%, with a persistent hematologic remission. Overall, three patients died while in remission, one due to a gastric cancer, one of senectus (at the age of 92) and the last one for an unspecified cause.

The median follow-up of the 18 patients is 10 years (range, 0.8-26), with a median OS not reached at the last follow-up, a 5-years OS estimated at 79%, a median relapse-free survival (RFS) not reached and a 5-year RFS estimated at 63% (Figure 1A, B).

To our knowledge, this is the largest series so far reported of Ph^+ ALL patients who did not undergo a SCT and discontinued TKI during the follow-up. The positive selection of cases, with a long-term observation period and no relapse during the observation period, is an intrinsic potential bias of this retrospective report. The only

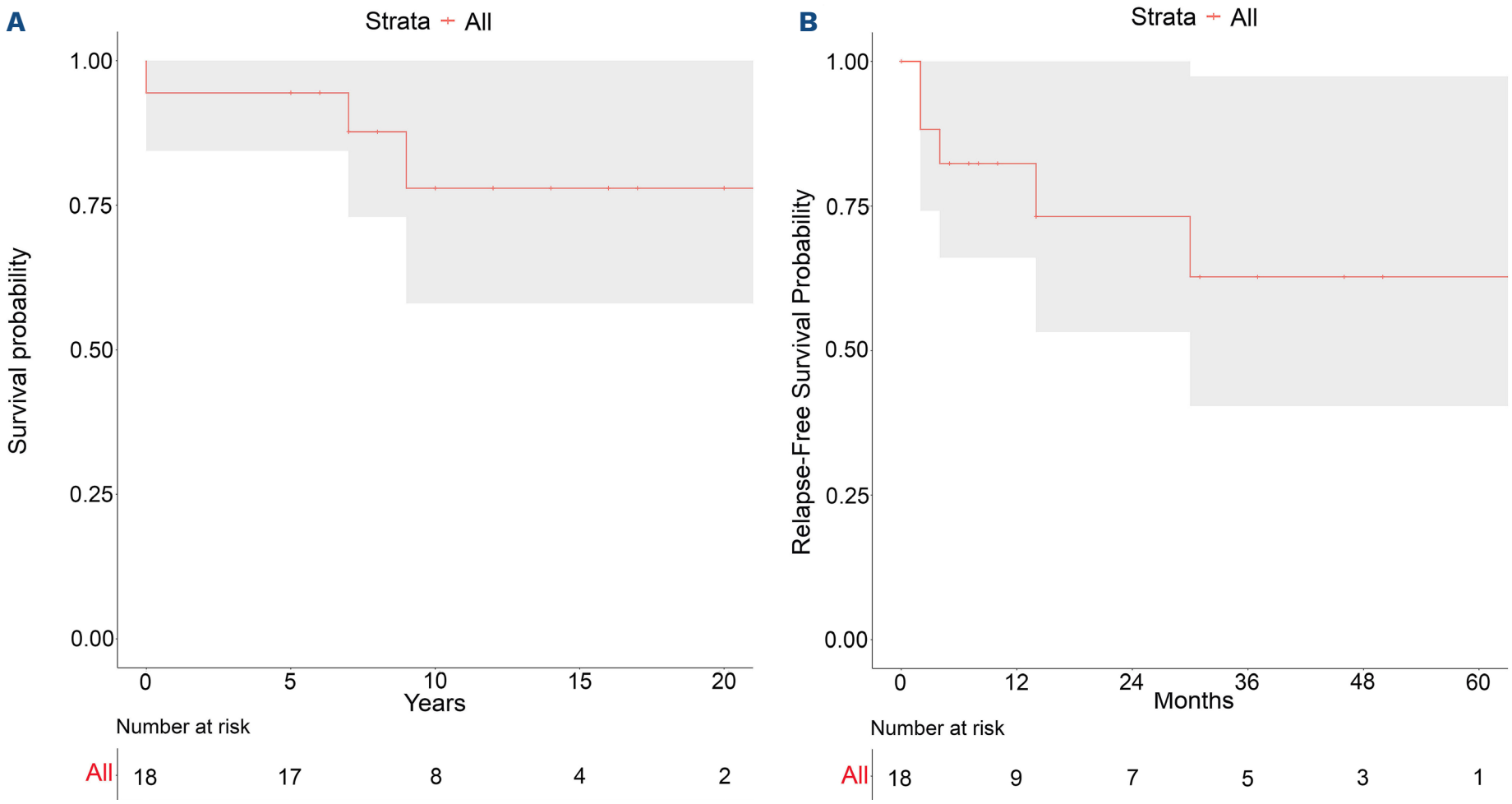

Figure 1. Kaplan-Meier curves. (A) Overall survival. (B) Relapse-free survival.

other report on the same topic is from the MD Anderson Cancer Center (MDACC) that published a monocentric retrospective series of nine patients.[7] In line with what is observed in the present series, three patients (33%) had a molecular relapse at a median of 6 months. All three resumed TKI treatment, and two regained a molecular response. After a median follow-up of 49 months, the TFR was not reached, and the 4-year TFR rate was 65%. It must be underlined that the present cohort and the one reported from MDACC are different mostly in terms of treatment received, since the MDACC cases received a hyper-CVAD polychemotherapy backbone plus imatinib in four patients, dasatinib in four and ponatinib in one, whereas in our cohort all patients underwent an induction with a TKI plus steroids alone or with mild chemotherapy (such as vincristine and anthracycline).

The possibility of offering a TFR in non-transplanted Ph$^+$ ALL patients is attractive for various reasons, including the possibility of reducing exposure to TKI and to off-target toxicities. Notably, in our cohort no morphologic relapse occurred, making the TFR attempt a feasible option. In patients in molecular relapse, TKI rechallenge was effective with all re-treated patients regaining a molecular remission. Although the number of patients in this cohort is relatively limited and retrospective, thus not allowing to draw definitive conclusions, it suggests that prolonged exposure to TKI treatment and an early achievement of molecular remission prior to discontinuation may be beneficial in terms of a longer TFR, mirroring a well-established concept in CML. Like in CML, it seems that Ph$^+$ ALL patients have a higher risk of TFR failure during the first period of discontinuation. Indeed, in our series most relapses occurred during the first 12 months.

Due to the retrospective nature of this report, the molecular monitoring of these patients after discontinuation was not homogeneous but most patients were evaluated at least every 3 months during the first year. It was performed according to the local clinical practice mostly relying on peripheral blood *BCR::ABL1/ABL1* levels without centralization, as carried out in national clinical trials. A minimal residual disease (MRD) analysis by immunoglobulin/T-cell receptor (Ig/TCR) gene rearrangement and by droplet digital polymerase chain reaction (ddPCR) on *BCR::ABL1/ABL1* could not be performed on retrospective samples due to the lack of available biologic material. In fact, our group previously reported that ddPCR allows to refine the quantifiability of MRD in a considerable proportion of patients with Ph$^+$ ALL.[8] Recent reports have also suggested that MRD evaluation by PCR or next-generation sequencing (NGS)-based assays for Ig/TCR rearrangements may provide a more accurate measure of clinically significant MRD than PCR for *BCR::ABL1* alone.[9-12] It could thus be pivotal in the setting of a TKI discontinuation program to identify patients who are more likely not to relapse upon discontinuation and to refine MRD monitoring thereafter to identify earlier patients who should restart TKI with the aim of preventing a hematologic relapse and of regaining a CMR status promptly.

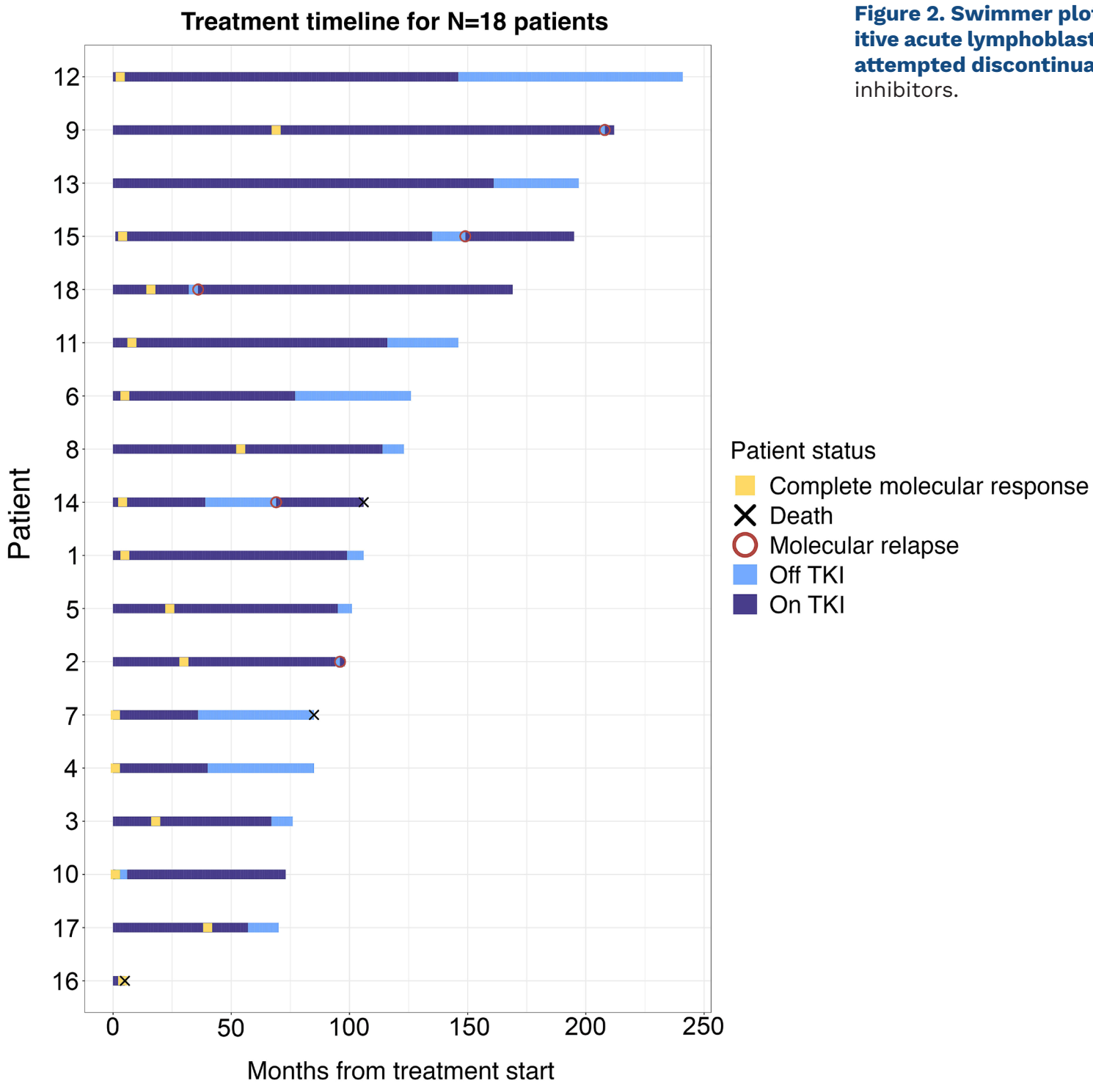

Figure 2. Swimmer plot of 18 Philadelphia-positive acute lymphoblastic leukemia patients who attempted discontinuation. TKI: tyrosine kinase inhibitors.

It should be underlined that blinatumomab in association with a TKI (dasatinib and ponatinib) has been associated with increased rates of CMR.[1,2,13,14] This will eventually lead to a greater number of patients who could attempt TKI discontinuation. In the D-ALBA study, we documented that the combination of dasatinib and blinatumomab in the absence of systemic chemotherapy exerted a marked host immunomodulatory effect with a significant increase in natural killer (NK), T-NK cells and a reduction of T regulatory cells,[15] which may ultimately lead to a better control of the disease. This immune modulation could potentially lower the rates of TFR failure.

A validation of these findings in a prospective clinical trial with frequent centralized molecular monitoring is highly needed to accurately identify the optimal subset of patients with Ph$^+$ ALL who could benefit most from TKI discontinuation. In addition, refined molecular analyses (i.e., bulk RNA sequencing, single cell RNA sequencing) may also help to identify molecular signatures of patients who may (or may not) be more likely to successfully stop treatment.

Authors

Matteo Dragani,[1*] Michela Ansuinelli,[2*] Cristina Papayannidis,[3*] Nicola Fracchiolla,[4] Valeria Cardinali,[5] Michele Cedrone,[6] Fabio Guolo,[7] Salvatore Perrone,[8] Prassede Salutari,[9] Elisabetta Todisco,[10,11] Robin Foà[2] and Sabina Chiaretti[2]

[1]Hematology and Cellular Therapy, IRCCS Ospedale Policlinico San Martino, Genova; [2]Hematology, Department of Translational and Precision Medicine, Sapienza University of Rome, Rome; [3]Istituto di Ematologia "Seràgnoli", IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna; [4]Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano; [5]Dipartimento di Medicina e Chirurgia, Università di Perugia, Ospedale "Santa Maria

della Misericordia", Perugia; [6]UOC Ematologia, Azienda Ospedaliera San Giovanni Addolorata, Rome; [7]Clinic of Hematology, Department of Internal Medicine (DiMI), University of Genova, Genova; [8]Department of Hematology, Polo Universitario Pontino, S.M. Goretti Hospital, Latina; [9]Department of Hematology, Ospedale Civile Spirito Santo, Pescara; [10]Onco-Hematology Division, IEO, European Institute of Oncology IRCCS, Milan and [11]Hematology Division, Busto Arsizio Hospital, ASST Valleolona, Varese, Italy

*MD, MA and CP contributed equally as first authors.

Correspondence:
M. DRAGANI - matteoemidio.dragani@hsanmartino.it

https://doi.org/10.3324/haematol.2024.286325

Received: July 24, 2024.
Accepted: December 30, 2024.
Early view: January 9, 2025.

Disclosures

No conflicts of interest to disclose.

Contributions

MD and MA analyzed data and wrote the manuscript. CP, NF, VC, MC, FG, SP, PS and ET provided clinical and followed patients. RF and SC designed research, analyzed data, wrote and critically revised the manuscript.

Funding

The authors wish to thank Associazione Italiana per la Ricerca sul Cancro (AIRC) 5x1000, Special Program Metastases (21198), Milan (Italy) (to RF), Progetti di Rilevante Interesse Nazionale (PRIN) Italia, 2022EC7LA project (to SC), Finanziamento Medi Progetti Universitari 2021 (to SC) (Sapienza University of Rome).

Data-sharing statement

Datasets are maintained in an electronic database at the Department of Translational and Precision Medicine, Sapienza University of Rome. Data are available from the corresponding author upon request.

References

1. Foà R, Bassan R, Vitale A, et al. Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. N Engl J Med. 2020;383(17):1613-1623.
2. Foà R, Bassan R, Elia L, et al. Long-term results of the dasatinib-blinatumomab protocol for adult Philadelphia-positive ALL. J Clin Oncol. 2024;42(8):881-885.
3. Stock W, Martinelli G, Stelljes M, et al. Efficacy of inotuzumab ozogamicin in patients with Philadelphia chromosome-positive relapsed/refractory acute lymphoblastic leukemia. Cancer. 2021;127(6):905-913.
4. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-984.
5. Deininger MW, Shah NP, Altman JK, et al. Chronic myeloid leukemia, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2020;18(10):1385-1415.
6. Martinelli G, Papayannidis C, Piciocchi A, et al. Extremely high rate of complete hematological response of elderly Ph+ acute lymphoblastic leukemia (ALL) patients by innovative sequential use of nilotinib and imatinib. A GIMEMA Protocol LAL 1408. Cancer Res. 2014;74(19 Suppl):5552.
7. Samra B, Kantarjian HM, Sasaki K, et al. Discontinuation of maintenance tyrosine kinase inhibitors in Philadelphia chromosome-positive acute lymphoblastic leukemia outside of transplant. Acta Haematol. 2021;144(3):285-292.
8. Ansuinelli M, Della Starza I, Lauretti A, et al. Applicability of droplet digital polymerase chain reaction for minimal residual disease monitoring in Philadelphia-positive acute lymphoblastic leukaemia. Hematol Oncol. 2021;39(5):680-686.
9. Giovanni C, Paola De L, Julia A, et al. Predictive value of minimal residual disease in Philadelphia-chromosome-positive acute lymphoblastic leukemia treated with imatinib in the European intergroup study of post-induction treatment of Philadelphia-chromosome-positive acute lymphoblastic leukemia, based on immunoglobulin/T-cell receptor and BCR/ABL1 methodologies. Haematologica. 2018;103(1):107-115.
10. Zuna J, Hovorkova L, Krotka J, et al. Minimal residual disease in BCR::ABL1-positive acute lymphoblastic leukemia: different significance in typical ALL and in CML-like disease. Leukemia. 2022;36(12):2793-2801
11. Short NJ, Jabbour E, Macaron W, et al. Ultrasensitive NGS MRD assessment in Ph+ ALL: prognostic impact and correlation with RT-PCR for BCR::ABL1. Am J Hematol. 2023;98(8):1196-1203.
12. Kim R, Chalandon Y, Rousselot P, et al. Significance of measurable residual disease in adult Philadelphia chromosome-positive ALL: A GRAAPH-2014 study. J Clin Oncol. 2024;42(26):3140-3150.
13. Jabbour E, Short NJ, Jain N, at al. Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: a US, single-centre, single-arm, phase 2 trial. Lancet Haematol. 2023;10(1):e24-e34.
14. Chiaretti S, Leoncin M, Elia L, et al. Comparison between dasatinib-blinatumomab vs ponatinib blinatumomab chemo-free strategy for newly diagnosed Ph+ acute lymphoblastic leukemia patients. Preliminary results of the GIMEMA ALLL2820 Trial. Blood. 2023;142(Suppl 1):4249.
15. Puzzolo MC, Radice G, Peragine N, et al. Host immune system modulation in Ph+ acute lymphoblastic leukemia patients treated with dasatinib and blinatumomab. Blood. 2021;138(22):2290-2293.