Leukemia (2020) 34:929–931
https://doi.org/10.1038/s41375-019-0591-9

LETTER

Chronic myelogenous leukemia

In Ph+BCR-ABL1^{P210+} acute lymphoblastic leukemia the e13a2 (b2a2) transcript is prevalent

Michele Baccarani[1] · Ilaria Iacobucci[2] · Sabina Chiaretti[3] · Robin Foà'[3] · Poonkuzhali Balasubramanian[4] · Elisabeth Paietta[5] · Letizia Foroni[6] · Sabine Jeromin[7] · Barbara Izzo[8] · Orietta Spinelli[9] · Neelam Varma[10] · Samia Menif[11] · Carolina Terragna[1] · Tulika Seth[12] · Audrey Bidet[13] · Daniel Coriu[14] · Francesca Lunghi[15] · Jiri Mayer[16] · Barbara Scappini[17] · Stephen Langabeer[18] · Jacqueline Maier[19] · Emma Burt[20] · Anna Candoni[21] · Francesco Albano[22] · Mario Luppi[23] · Irena Zupan[24] · Thomas Lion[25] · Renata Zadro[26] · Francesco di Raimondo[27] · Behzad Poopak[28] · Giovanna Rege-Cambrin[29] · Mario Annunziata[30] · Ana Ayala[31] · Victor Salinas-Viedma[32] · Ana Ines Prado[33] · Benedict Milner[34] · Sara Galimberti[35] · Jeroen Janssen[36] · Valentina Polli[37] · Lorenzo Comba[38] · Beatrice Borsellino[39] · Ombretta Annibali[40] · Monica Crugnola[41] · Francesco Passamonti[42]

Received: 10 July 2019 / Revised: 11 September 2019 / Accepted: 25 September 2019 / Published online: 8 October 2019

To the Editor:

Philadelphia-chromosome positive (Ph+), BCR-ABL1+ acute lymphoblastic leukemia (ALL) is a distinct entity that is characterized by specific genomic alterations, low sensitivity to chemotherapy, unstable responsiveness to tyrosine kinase inhibitors (TKIs), and a poor prognosis [1–3]. The frequency of Ph+ ALL varies with age, ranging from <10% in children to about 50% in the elderly [3, 4]. Ph+ ALL is driven by a reciprocal translocation between chromosome 9 and chromosome 22, leading to the formation of hybrid fusion genes, that are all leukemogenic but can vary depending on the site of the breakpoints [5, 6]. The most common gene, that accounts for about 70–80% of all cases, results from the fusion of BCR exon 1 on chromosome 22 with ABL1 exon 2 on chromosome 9, much more rarely with ABL1 exon 3. The resulting e1a2 (or e1a3) fusion gene codes for a leukemogenic protein of 185–190 kd (P190). In 20–30% of cases, the breakpoint on chromosome 22 is downstream to BCR exon 1, resulting from the fusion of ABL1 exon 2 on chromosome 9 with either BCR exon 13 or BCR exon 14 on chromosome 22. The resulting fusion transcripts are named e13a2 (also known as b2a2), and e14a2 (also known as B3A2), respectively. The fusion e13a2 can give rise to only one transcript (e13a2) and one leukemogenic protein of 210 kd (P210). The fusion e14a2 usually give rise to one transcript (e14a2) that is longer, and codes for a leukemogenic protein that is also called P210, but has 25 additional amino acids and different secondary structure elements [5, 6]. Sometimes the e14a2 fusion gene, that retains BCR exon 13, can also generate a minor amount of e13a2 transcript, because of alternative splicing mechanisms. Therefore, the BCR-ABL1^{P210+} leukemias have two different molecular signatures:e13a2, and e14a2 (+_e13a2). The frequency of the two signatures has never been systematically investigated. In a paper from the MD Anderson Cancer Center it was reported that of 17 patients with Ph+, BCR-ABL1^{P210+} 76% expressed e13a2 [7].

In a previous international study of the frequency of the two transcripts in 45,503 patients with newly diagnosed BCR-ABL1^{P210+} chronic myeloid leukemia (CML), it was found that 17,216 patients (37.9%) expressed only e13a2, with a proportion that varied with age, from 39.6% in children and adolescents down to 31.6% in the elderly, and with sex, from 36.5% in females up to 39.2% in males [8]. To assess the frequency of e13a2 in BCR-ABL1^{P210+} ALL, we collected the molecular data from 849 patients with Ph+, BCR-ABL1^{P210+} ALL, from 39 Institutions, as a first quick step of a project that was designed to evaluate the clinical and biological characteristics and the outcomes of BCR-ABL1+ ALL according to the different transcripts. Completing the project will take more time and more resources, and we report here the first data set: 497 patients (58.5%) expressed only e13a2, a proportion that was significantly higher than the proportion of e13a2 that was found in newly diagnosed chronic phase CML (37.9%) (Fisher's exact test, two-sided, p value < 0.0001). This difference cannot be explained by age; indeed the frequency of Ph+ ALL increases with age and is highest

✉ Michele Baccarani
michele.baccarani@unibo.it

Extended author information available on the last page of the article.

in the elderly, where the frequency of e13a2 in CML is the lowest [3, 4, 8]. The finding that the distribution of the different breakpoints in BCR-ABL1 fusion gene is not by chance, being significantly different between CML and Ph+ ALL is of interest. While we are collecting data to compare the characteristics, the response to therapy and the outcomes according to transcript, other important questions, are unanswered. First, why is the distribution different, is the cause related to the cell where the translocation occurs (a multipotent stem cell versus a committed lymphoid progenitor)? Is it due to a different chromatine structure that may influence the position of the breakpoint and the formation of the hybrid gene [9], or to an aberrant activity of the machinery for V(D)J or class switch recombination, or to different DNA-repair mechanisms, or to a microenvironment with a different oxygen tension? Second, what are the biological and clinical consequences of the difference in transcript types, the e13a2 gene being possibly associated with a minor sensitivity to TKIs in CML [8], and at the same time being prevalent in an aggressive leukemia like ALL, that is only temporarily sensitive to TKIs [10–12]? Third, is the transcription efficacy of the two fusion genes identical, or is the turnover of the two mRNAs different, resulting in different amounts of transcript? Fourth, have the two proteins the same leukemogenic potency, have they the same turnover, is the cellular level identical? Fifth, is the sensitivity of the two chimeric proteins to TKIs different? Sixth, is the immunogenicity of the two chimeric transcripts and of the two resulting proteins identical? Of course all these questions need to be addressed also for the more common form of Ph+, BCR-ABL1^{P190+} ALL (e1a2 or e1a3) [13–15], not forgetting that P190 can also cause CML, although rarely [8]. The answer to these questions may help to optimize the management of Ph+ ALL patients, and also to improve our knowledge on the relationships of genes and gene/protein expression with leukemia.

Acknowledgements This work was supported in part by the European Leukemia Net Foundation and by AIRC 5×1000 (21198). The technical assistance of Mrs Chiara Ferri is kindly acknowledged.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med. 2006;354:166–78.
2. Ravandi F, Kebriaei P. Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematol Oncol Clin North Am. 2009;23:1043. vi
3. Chiaretti S, Vitale A, Cazzaniga G, Orlando SM, Silvestri D, Fazi P, et al. Clinico-biologic features of 5202 patients with acute lymphoblastic leukemia enrolled in the Italian AIEOP and GIMEMA protocols and stratified in age cohorts. Haematologica. 2013;98:1702–10.
4. Burmeister T, Schwartz S, Bartram CR, Gokbuget N, Hoelzer D, Thiel S. Patients' age and BCR-ABL frequency in adult B-cell precursor ALL: a retrospective analysis from the GMALL study group. Blood. 2008;112:918–9.
5. Melo JV. The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype. Blood. 1996;88:2375–84.
6. Chereda B, Melo JV. The biology and pathogenesis of chronic myeloid leukemia. In: Hehlmann R, editor. Chronic myeloid leukemia. Switzerland: Springer International Publishing; 2016. p. 17–40.
7. Ravandi F, O'Brien S, Cortes JE, Thomas DM, Garris R, Faderl S, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer. 2015;121:4158–64.
8. Baccarani M, Castagnetti F, Gugliotta G, Rosti G, Soverini S, Albeer A, et al. The proportion of different BCR-ABL1 transcript types in chronic myeloid leukemia. an international overview. Leukemia. 2019. https://doi.org/10.1038/s41375-018-0341-4.
9. Hai A, Kizilbash NA, Zaidi SH, Alruwaili J, Shahzad K. Differences in structural elements of Bcr-Abl oncoprotein isoforms in chronic myelogenous leukemia. Bioinformation. 2014;10:108–14.
10. Vignetti M, Fazi P, Cimino G, Martinelli G, Di Raimomdo F, Ferrara F, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell' Adulto (GIMEMA) LAL0201-B protocol. Blood. 2007;109:3676–8.
11. Foà R, Vitale A, Vignetti M, Meloni G, Guarini A, De Propris MS, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2011;118:6521–8.
12. Malagola M, Papayannidis C, Baccarani M. Tyrosine kinase inhibitors in Ph+ acute lymphoblastic leukaemia: facts and perspectives. Ann Hematol. 2016;95:681–93.
13. Score J, Calasanz MJ, Ottman O, Pane F, Yeh RF, Sobrinho-Simoes MA, et al. Analysis of genomic breakpoints in p190 and p210 BCR-ABL indicate distinct mechanisms of formation. Leukemia. 2010;24:1742–50.
14. Reckel S, Hamelin R, Georgeon S, Armand F, Jolliet Q, Chiappe D, et al. Differences in structural elements of bcr-Abl oncoprotein isoforms in chronic myelogenous leukemia. Leukemia. 2017;31:1502–15.
15. Cutler J, Tahir R, Sreenivasamurthy SK, Mitchell C, Renuse S, Nirujogi RS. Differential signaling through p190 and p210 BCR-ABL fusion proteins reveales by interactome and phosphoproteome analysis. Leukemia. 2017;31:1513–24.

Affiliations

Michele Baccarani[1] · Ilaria Iacobucci[2] · Sabina Chiaretti[3] · Robin Foà'[3] · Poonkuzhali Balasubramanian[4] · Elisabeth Paietta[5] · Letizia Foroni[6] · Sabine Jeromin[7] · Barbara Izzo[8] · Orietta Spinelli[9] · Neelam Varma[10] · Samia Menif[11] · Carolina Terragna[1] · Tulika Seth[12] · Audrey Bidet[13] · Daniel Coriu[14] · Francesca Lunghi[15] · Jiri Mayer[16] · Barbara Scappini[17] · Stephen Langabeer[18] · Jacqueline Maier[19] · Emma Burt[20] · Anna Candoni[21] · Francesco Albano[22] · Mario Luppi[23] · Irena Zupan[24] · Thomas Lion[25] · Renata Zadro[26] · Francesco di Raimondo[27] · Behzad Poopak[28] · Giovanna Rege-Cambrin[29] · Mario Annunziata[30] · Ana Ayala[31] · Victor Salinas-Viedma[32] · Ana Ines Prado[33] · Benedict Milner[34] · Sara Galimberti[35] · Jeroen Janssen[36] · Valentina Polli[37] · Lorenzo Comba[38] · Beatrice Borsellino[39] · Ombretta Annibali[40] · Monica Crugnola[41] · Francesco Passamonti[42]

1 Institute of Hematology "L. and A. Seràgnoli", Bologna University, Bologna, Italy

2 Department of Pathology, St. Jude Children's Cancer Research Hospital, Memphis, TN, USA

3 Heamatology, Department of Precision and Translational Medicine, Sapienza University, Rome, Italy

4 Christian Medical College, Vellore, India

5 ECOG-ACRIN Leukemia Laboratory, Montefiore Medical Center, New York, NY, USA

6 Hammersmith Hospital, London, UK

7 MLL Munich, Leukemia Laboratory GmbH, Munich, Germany

8 Federico II University, Naples, Italy

9 ASST Papa Giovanni XXIII, Bergamo, Italy

10 PGIMER, Chandigarh, India

11 Institut Pasteur, Tunis, Tunisie

12 AIIMS, New Delhi, India

13 CHU Bordeaux-Haut Léveque, Bordeaux, France

14 Fundeni Clinical Institute, Bucharest, Romania

15 San Raffaele University, Milan, Italy

16 University Hospital and Masaryk University, Brno, Czech Republic

17 AOU Careggi, Florence, Italy

18 St. James Hospital, Dublin, Ireland

19 Universitat Leipzig, Leipzig, Germany

20 The Royal London Hospital, London, UK

21 Udine University, Udine, Italy

22 Bari University, Bari, Italy

23 Modena and Reggio Emilia University, Modena, Italy

24 University Clinical Center, Ljubljana, Slovenia

25 Children's Cancer Research Institute, Wien, Austria

26 University Hospital Center, Zagreb, Croatia

27 Catania University, Catania, Italy

28 Islamic Azada University and Payvand Lab, Tehran, Iran

29 Orbassano Hospital, Turin University, Turin, Italy

30 Cardarelli Hospital, Naples, Italy

31 Universidad Nacional de Asuncion, San Lorenzo, Paraguay

32 Instituto de Prevision Social, Asuncion, Paraguay

33 Hospital Maciel, Montevideo, Uruguay

34 NHS-Grampian, Aberdeen, UK

35 Pisa University, Pisa, Italy

36 Department of Hematology, VUMC, Amsterdam, The Netherlands

37 Infermi Hospital, Rimini, Italy

38 S.C. Hematology, Cuneo, Italy

39 Ancona University, Ancona, Italy

40 Campus University, Rome, Italy

41 University Hospital, Parma, Italy

42 Varese University, Varese, Italy