High-risk additional cytogenetic aberrations in a Dutch chronic phase chronic myeloid leukemia patient population

Several chromosomal aberrations detected in addition to the pathognomonic Philadelphia chromosome (Ph) at diagnosis confer a poor prognosis in chronic myeloid leukemia (CML) chronic phase (CP) patients and herald earlier progression to accelerated phase (AP) or blast crisis (BC), and CML-related death.[1-3] Their prognostic significance has been established both at diagnosis and when emerging in the course of the disease. Since not all clones have the same clinical relevance, several classifications have been proposed in the recent literature to define additional cytogenetic aberrations (ACA) presenting a higher risk of inferior outcomes.[4-8] The conventional classification in "major" and "minor route" ACA was based on their prevalence and appeared to be too restricted to cover all "high-risk" ACA (HR-ACA). Besides four major-route ACA (trisomy 8, isochromosome 17q, additional Ph chromosome and trisomy 19 while excluding loss of Y), five other HR-ACA were identified (trisomy 21, 3q26.2 rearrangements, monosomy 7/7q-, 11q23 rearrangements, and complex karyotypes) in a recent study of CML-CP patients.[8] In this study, their presence often preceded an increase in blast percentage and thereby anticipated progression. However, one study did not observe a prognostic impact of trisomy 8 or an additional Ph chromosome when occurring as a single ACA and only heralded inferior outcomes when in combination with other concurrent ACA.[5] These discrepant results may be due to low observation numbers at diagnosis as HR-ACA remain relatively rare and are detected in less than 3% of *de novo* CML-CP patients.[8-10] Consequently, the cohort sizes of previous studies of patients with HR-ACA have been relatively small and verification of findings is necessary. Here, we aim to assess the prevalence of ACA at diagnosis and their clinical impact in a Dutch nationwide patient cohort, with a focus on the recently proposed HR-ACA classification.[8] In addition, we intend to assess the relation of HR-ACA to the EUTOS long-term survival (ELTS) score at diagnosis and to assess the impact of chromosomal aberrations on hematological toxicity (hemtox) of first-line tyrosine kinase inhibitor (TKI) treatment.

Data were derived from a real-world population-based CML registry in the Netherlands (PHAROS-CML registry combined with HemoBase) covering a nationwide patient cohort diagnosed with CML between 2008 and 2014.[11] We included all adult CML-CP patients with an evaluable cytogenetic assessment at diagnosis. HR-ACA were defined following Hehlmann *et al.* (*+8, i(17q), +Ph, +19, +21, 3q26.2, -7/7q-, 11q23.2* and *complex karyotype*; present in Ph-positive cells).[8] Other ACA in Ph-positive cells were classified as low-risk ACA (LR-ACA). The emergence of chromosomal aberrations was also assessed during the first 24 months of TKI treatment, including clonal chromosomal aberrations in Ph-negative cells (CCA/Ph$^-$). AP and BC were defined as described in the ELN recommendations.[12] Hemtox was defined as *de novo* anemia, thrombocytopenia and/or leukopenia CTC grade 3 or higher, emerging during first-line TKI therapy.

Survival analysis was performed with Kaplan-Meier estimates and the log-rank test was used to compare subgroups. Progression-free survival (PFS) was defined as the time from diagnosis until progression to AP/BC or death. Patients were censored at last follow-up visit. CML-related death was defined as death preceded by CML progression and was assessed using the cumulative incidence competing risk (CICR) method in which death of any other cause was considered as a competing event. Response milestones (complete hematological response [CHR], complete cytogenetic response [CCyR] and major molecular response [MMR]) were defined in accordance with the ELN recommendations.[12] The achievement of CCyR, MR2.0 (*BCR::ABL1* <1%IS) or MMR was assessed with the CICR method in which progression or death were considered as a competing event. A Cox proportional hazards model was used to assess different predictors for PFS including age, ELTS score (as a numeric variable) and the presence of HR-ACA at diagnosis. The X^2 test was used to assess differences in hemtox across subgroups, only considering complete cases. The Medical Ethics Committee of the Erasmus Medical Center in Rotterdam approved this study and the exemption from informed consent. The study was conducted in accordance with the Declaration of Helsinki.

A total of 398 CML-CP patients were included in this analysis. Thirty ACA (8%) were detected at diagnosis of which 15 were HR-ACA (4%) (Figure 1). The most frequent HR-ACA were trisomy 8 and an extra copy of Ph chromosome. Loss of the Y chromosome (-Y) as a solitary additional aberration in Ph-positive cells was observed in ten patients and was not designated as ACA since several studies did not report any clinical impact of this aberration.[5,8]

Patients with HR-ACA at diagnosis were younger than patients without HR-ACA, with a median age of 49 years (interquartile range [IQR], 34-61 years) *versus* 57 years ([IQR], 43-68 years) at diagnosis, respectively (P=0.198). Other

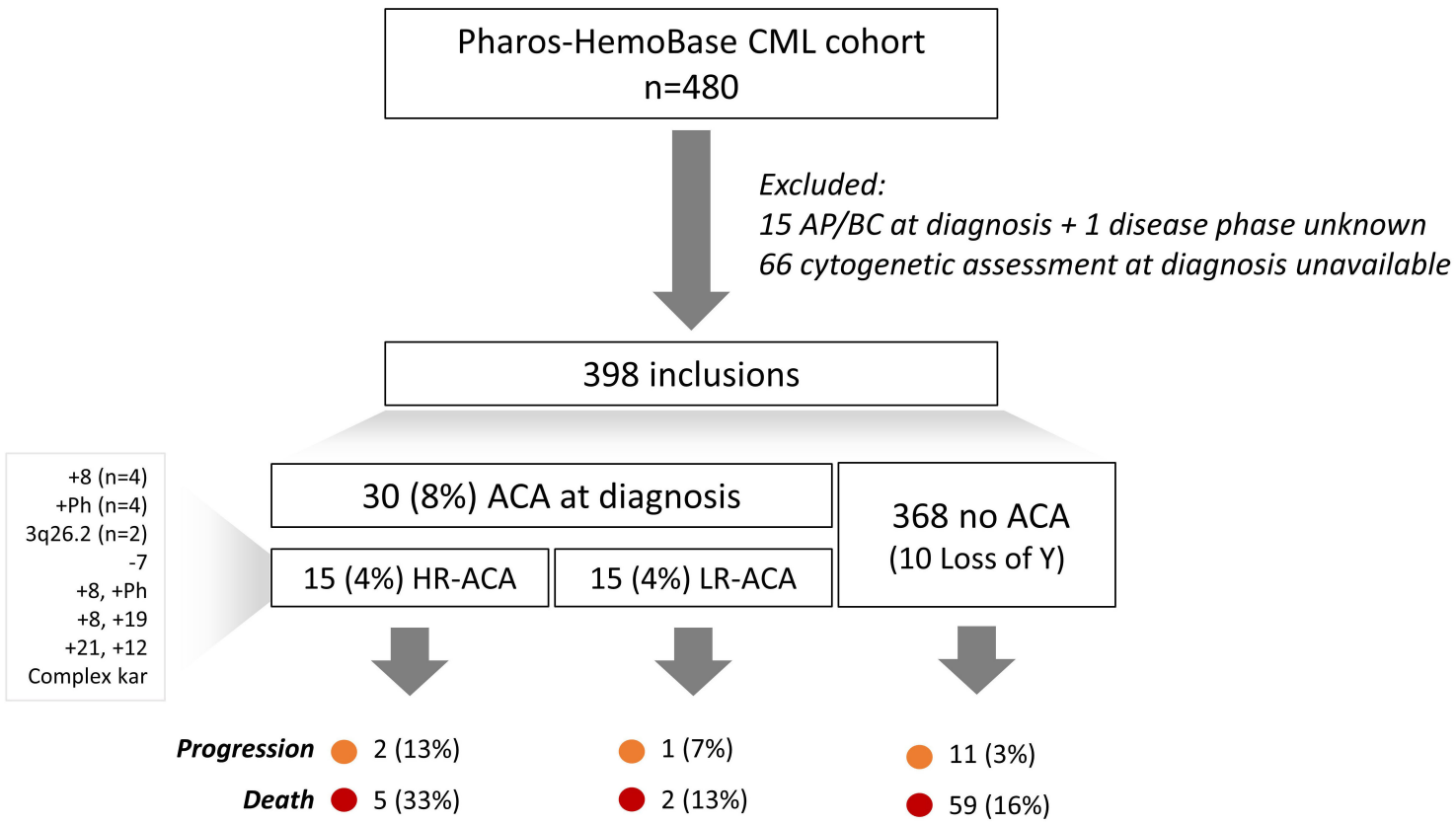

Figure 1. Inclusion flowchart and prevalence of (additional) cytogenetic aberrations found in the Pharos-HemoBase chronic myloid leukemia patient population at diagnosis. AP/BC: accelerated phase or blast crisis; ACA: additional cytogenetic aberrations; HR: high-risk; LR: low-risk; kar: karyotype.

baseline characteristics were comparable between subgroups, including the ELTS score at diagnosis and the use of second generation TKI as first line treatment. There was no statistically significant association between ELTS categories and the presence of HR-ACA using the X^2 test (*P*=0.168), nor was there a significant difference in the mean ELTS score in patients with or without HR-ACA using the Student's *t*-test (*P*=0.400).

During the first 24 months of TKI treatment, one or more follow-up cytogenetic assessments were done in 257 patients. In these patients, four patients (2%) had newly emerging ACA in the context of disease progression, and 31 patients (12%) developed CCA/Ph$^-$. Most frequent CCA/Ph$^-$ were –Y (n=12), +8 (n=11) and -7/7q- (n=4). Transition to myelodysplasia or acute myeloid leukemia was not observed during further follow-up of these patients.

Five-year PFS for patients with HR-ACA, with LR-ACA or without ACA was 60% (95% confidence interval [CI]: 40-91), 87% (95% CI: 71-100) and 85% (95% CI: 81-89), respectively, with a median follow-up duration of 5 years (IQR, 4-8 years) (Figure 2A). Of note, in patients with ACA, all events of progression or death occurred within 3 years from time of diagnosis. After further stratification based on HR-ACA and the ELTS score at diagnosis, an inferior PFS was noted in patients with HR-ACA in combination with an intermediate or high ELTS score (Figure 2B). In line with PFS results, the cumulative incidence of CML-related mortality was higher in patients with HR-ACA than patients without HR-ACA (13% *vs.* 3% at 5 years; *P*<0.032). No difference in PFS was observed for patients with solitary –Y or with emerging CCA/Ph$^-$ compared to patients without aberrations (*Online Supplementary Figure S1*). Again, when specifically assessing non –Y CCA/Ph$^-$, no difference in PFS was noted (*graph not shown*; *P*=0.703).

In a univariable Cox regression analysis, age, ELTS score and the presence of HR-ACA were predictive for PFS, with a hazard ratio (HR)=1.06, 95% CI: 1.04-1.08; HR=2.09, 95% CI: 1.39-3.15 and HR=2.81; 95% CI: 1.22-6.49, respectively (*Online Supplementary Table S1*). We fitted a multivariable model with ELTS score and HR-ACA, and excluded age since it is already part of the ELTS score calculation. The HR for PFS of HR-ACA and ELTS score were HR=3.13, 95% CI: 1.34-7.31 and HR=2.06, 95% CI: 1.37-3.11, respectively.

Regarding the achievement of the ELN response milestones, CHR at 90 days was achieved in 80% *versus* 87% of patients with *versus* without HR-ACA, respectively (*P*=0.428). The cumulative incidence of CCyR or MR2.0 at 6 months was 10% (95% CI: 0-30) *versus* 38% (95% CI: 32-43) in patients with *versus* without HR-ACA, respectively (*P*=0.261). The cumulative incidence of MMR at 12 months was 22% (95% CI: 0-51) *versus* 50% (95 % CI: 44-57) in patients with *versus* without HR-ACA, respectively (*P*=0.045). Of note, all HR-ACA patients who eventually presented with disease progression, failed to achieve the MR2.0 or MMR ELN milestone in time.

In a final exploratory analysis, we assessed the occurrence of hemtox on first-line tyrosine kinase inhibitor (TKI) treatment. Patients with HR-ACA at diagnosis had significantly more hemtox than those without any ACA (39% *vs.* 16%; *P*=0.030), while this difference was not observed for pa-

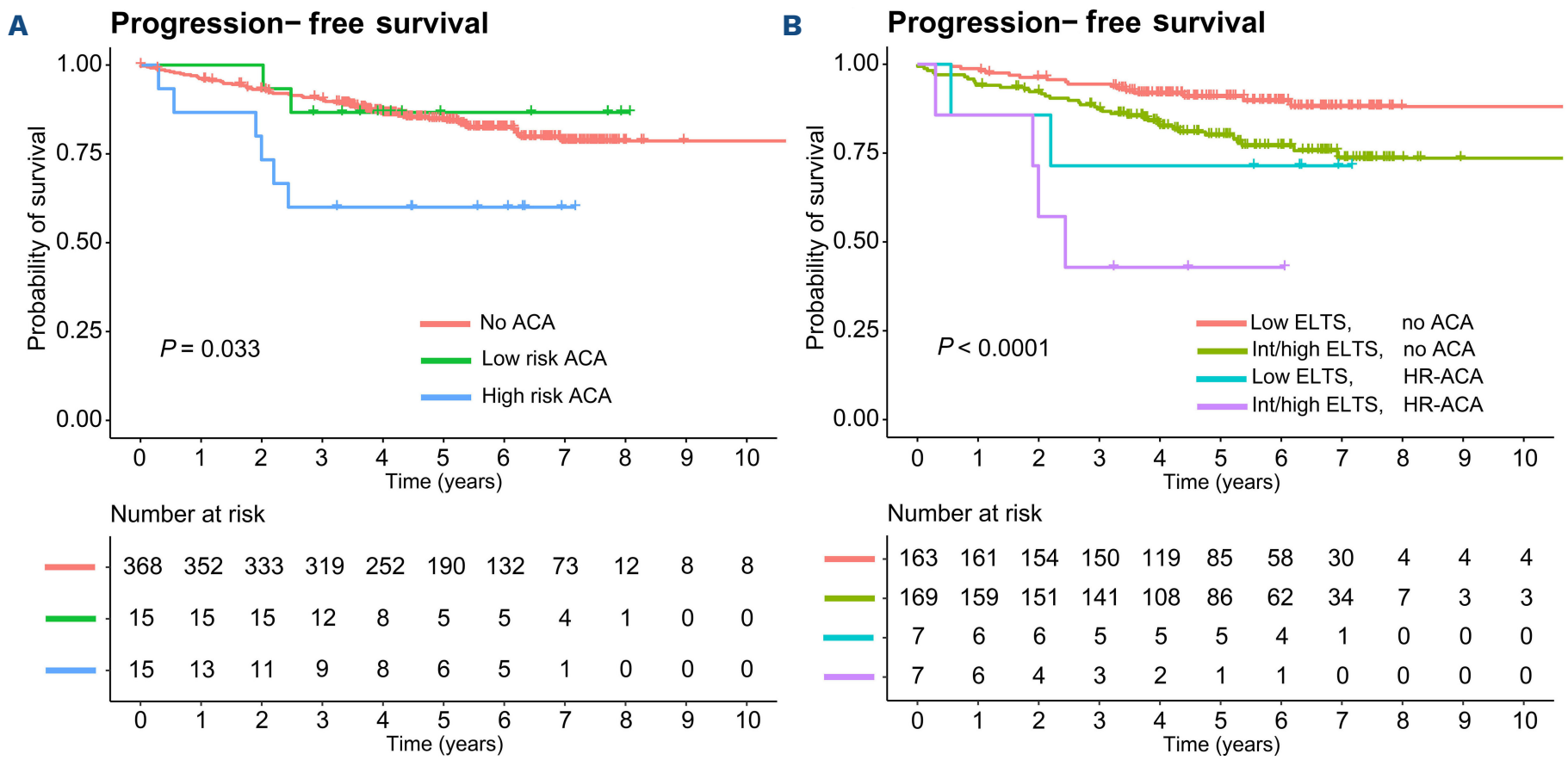

Figure 2. Progression-free survival Kaplan-Meier estimates. (A) Subgroups based on the presence of low-risk (LR) or high-risk (HR) additional cytogenetic aberrations (ACA). (B) Subgroups based on the presence of high-risk ACA and the EUTOS long-term survival (ELTS) score.

tients with LR-ACA (10% *vs.* 16%; *P*=0.607). Patients with CCA/Ph$^-$ emerging during the first 24 months of TKI treatment, also experienced more hemtox than patients without CCA/Ph$^-$ (32% *vs.* 16%; *P*=0.026). In CCA/Ph$^-$ patients, hemtox was mostly observed in case of +8 and/or -7/7q- (7/15, 47%), and in lesser extent in case of –Y (2/12, 17%). In both groups (HR-ACA and CCA/Ph- patients) the difference in hemtox was mainly due to an increased incidence of thrombocytopenia, with or without concomitant anemia or leukopenia.

In conclusion, our results support the recently proposed ACA risk classification.[8] HR-ACA at diagnosis were associated with inferior responses, and a significantly higher probability of progression and (CML-related) death, while patients with LR-ACA had a PFS comparable to that of other CML-CP patients. Furthermore, HR-ACA at diagnosis remained independently predictive for PFS in a multivariable regression model including ELTS score, which is in line with a previous analysis.[10] In contrast with HR-ACA, the emergence CCA/Ph$^-$ did not have an impact on PFS in our cohort. The prognostic significance of this entity remains controversial, more specifically for non –Y CCA/Ph$^-$.[13,14]

Additionally, our data suggest that patients with HR-ACA at diagnosis or with CCA/Ph$^-$ emerging during TKI treatment, have a higher risk of TKI-related hemtox. CCA/Ph$^-$ might interfere with normal (Ph$^-$) hematopoiesis, predisposing to TKI-related hemtox. This is in line with previous studies showing an increased risk of development of myelodysplastic syndrome from a CCA/Ph$^-$ clone.[15,16]

Taken together, follow-up cytogenetic evaluation after diagnosis is warranted in case of failure to achieve molecular milestones in order to evaluate clonal progression,[17] and also in case of hematological toxicity to evaluate emergence of CCA/Ph$^-$, even when molecular response is optimal. Our results on their own should be interpreted with caution since the number of patients with HR-ACA and CCA/Ph$^-$ was low. However, our study contributes to the accumulating evidence that implies that patients with HR-ACA at diagnosis, particularly with a high ELTS, may benefit from a more aggressive treatment strategy with a second-generation TKI and an earlier switch to allogeneic stem cell transplantation if the response to TKI is unsatisfactory or results in significant hematological toxicity.

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Disclosures

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Contributions

CK performed the main data-analysis and wrote the first draft of the manuscript. CK, PW and HB evaluated reported karyotypes and cytogenetic aberrations. All authors revised and approved the final version of the manuscript.

Data-sharing statement

Data can be made available on request to other researchers, when in collaboration with the Dutch Cancer Registry, which is the owner of the data.

References

1. Anastasi J, Feng J, Le Beau MM, Larson RA, Rowley JD, Vardiman JW. The relationship between secondary chromosomal abnormalities and blast transformation in chronic myelogenous leukemia. Leukemia. 1995;9(4):628-633.
2. Marktel S, Marin D, Foot N, et al. Chronic myeloid leukemia in chronic phase responding to imatinib: the occurrence of additional cytogenetic abnormalities predicts disease progression. Haematologica. 2003;88(3):260-267.
3. Cortes JE, Talpaz M, Giles F, et al. Prognostic significance of cytogenetic clonal evolution in patients with chronic myelogenous leukemia on imatinib mesylate therapy. Blood. 2003;101(10):3794-3800.
4. Mitelman F, Levan G, Nilsson PG, Brandt L. Non-random karyotypic evolution in chronic myeloid leukemia. Int J Cancer. 1976;18(1):24-30.
5. Wang W, Cortes JE, Tang G, et al. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. Blood. 2016;127(22):2742-2750.
6. Gong Z, Medeiros LJ, Cortes JE, et al. Cytogenetics-based risk prediction of blastic transformation of chronic myeloid leukemia in the era of TKI therapy. Blood Adv. 2017;1(26):2541-2552.
7. Alhuraiji A, Kantarjian H, Boddu P, et al. Prognostic significance of additional chromosomal abnormalities at the time of diagnosis in patients with chronic myeloid leukemia treated with frontline tyrosine kinase inhibitors. Am J Hematol. 2018;93(1):84-90.
8. Hehlmann R, Voskanyan A, Lauseker M, et al. High-risk additional chromosomal abnormalities at low blast counts herald death by CML. Leukemia. 2020;34(8):2074-2086.
9. Fabarius A, Leitner A, Hochhaus A, et al. Impact of additional cytogenetic aberrations at diagnosis on prognosis of CML: long-term observation of 1151 patients from the randomized CML study IV. Blood. 2011;118(26):6760-6768.
10. Clark RE, Apperley JF, Copland M, Cicconi S. Additional chromosomal abnormalities at chronic myeloid leukemia diagnosis predict an increased risk of progression. Blood Adv. 2021;5(4):1102-1109.
11. Geelen IGP, Thielen N, Janssen JJWM, et al. Treatment outcome in a population-based, 'real-world' cohort of patients with chronic myeloid leukemia. Haematologica. 2017;102(11):1842-1849.
12. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-984.
13. Deininger M, Cortes J, Paquette R, et al. The prognosis for patients with chronic myeloid leukemia who have clonal cytogenetic abnormalities in Philadelphia chromosome-negative cells. Cancer. 2007;110(7):1509-1519.
14. Issa G, Kantarjian H, Gonzalez G, et al. Clonal chromosomal abnormalities appearing in Philadelphia chromosome-negative metaphases during CML treatment. Blood. 2017;130(19):2084-2091.
15. Bumm T, Müller C, Al-Ali H, et al. Emergence of clonal cytogenetic abnormalities in Ph-cells in some CML patients in cytogenetic remission to imatinib but restoration of polyclonal hematopoiesis in the majority. Blood. 2003;101(5):1941-1949.
16. Jabbour E, Kantarjian HM, Abruzzo LV, et al. Chromosomal abnormalities in Philadelphia chromosome negative metaphases appearing during imatinib mesylate therapy in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Blood. 2007;110(8):2991-2995.
17. Geelen IGP, Thielen N, Janssen JJWM, et al. Omitting cytogenetic assessment from routine treatment response monitoring in chronic myeloid leukemia is safe. Eur J Haematol. 2018;100(4):367-371.