High incidence of minor and micro breakpoints in Chronic Myeloid Leukaemia with additional cytogenetic abnormalities at diagnosis – the Western Australian series

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ARTICLE INFO

Keywords:
Chronic Myeloid Leukaemia
Cytogenetics
Leukaemia
Tyrosine kinase inhibitors
Additional chromosomal abnormalities

ABSTRACT

Introduction and objective: Chronic Myeloid Leukaemia (CML) is defined by the presence of the Philadelphia chromosome, a balanced translocation between chromosomes 9 and 22 that results in the constitutively active tyrosine kinase, BCR-ABL1. Additional chromosomal abnormalities (ACAs) at diagnosis occur in 5–10% of CML patients, and are important for prognosis. They are classified as major or minor route. The purpose of our study was to determine the frequency and type of ACAs in 193 newly diagnosed CML patients, and to evaluate patient characteristics, treatment response, and survival.

Methods: Medical records, in conjunction with data from the PathWest cytogenetics and molecular laboratories, were analysed.

Results: ACAs were present in 14 (7.3%) of patients at diagnosis. Seven patients had major-route abnormalities, with additional chromosome 8 (+8) the most common. All patients were treated with tyrosine kinase inhibitors (TKIs). Three patients presented in blast crisis; two patients have died. Of note, there was a high incidence of the rare minor and micro BCR-ABL1 fusion transcripts.

Conclusions: Frequency of ACAs at diagnosis was similar to that of previous reports. These patients consist a higher-risk cohort, and require individualised treatment, with consideration of frontline and secondary TKIs, adjunct chemotherapy, novel agents, and allogeneic stem cell transplant.

1. Introduction

The understanding and treatment of Chronic Myeloid Leukaemia (CML) is one of the success stories of cytogenetics. Its dependence upon the chimaeric BCR-ABL1 protein has led to the development of BCR-ABL1 tyrosine kinase inhibitors (TKIs). The BCR-ABL1 protein results in constitutive tyrosine kinase activity and is a product of the Philadelphia chromosome (Ph), characterised by t(9;22)(q34;q11) [1].

Additional cytogenetic abnormalities (ACAs) occur in 5–10% of patients [2]. Of these, major route changes (+8, +19, i(17q), ider(22)t (9;22)(q34;q11)) have adverse prognostic value; minor route changes (inversions, translocations) have not yet proved to be significant for progression [3].

Three breakpoint cluster regions in the BCR gene have been described: major (M-BCR), minor (m-BCR) and micro (μ-BCR). M-BCR occurs in the majority of CML patients, with only 1–2% demonstrating non-major breakpoints at diagnosis [4] (including the rare micro-breakpoints). These non-major breakpoints are associated with increased resistance to TKIs and increased progression to blast phase [4].

The use of TKIs and development of newer agents have markedly reduced the role of the allograft; outcomes for CML patients have improved significantly, such that survival is comparable to that of the general population [5]. However, ACAs at diagnosis and non-major breakpoint cluster regions are two potential high-risk factors [3,4] and are important considerations for the future management of CML. Due to their infrequency, the literature on these two factors is relatively sparse.

Our study includes all CML patients presenting with ACAs in Western

Abbreviations: CML, Chronic myeloid leukaemia; TKI, Tyrosine kinase inhibitor; ACA, Additional chromosomal abnormalities.

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https://doi.org/10.1016/j.lrr.2022.100344
Received 28 June 2022; Received in revised form 3 August 2022; Accepted 11 August 2022
Available online 13 August 2022

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Australia, a state with a population of 2.7 million with a land mass of 2.65 million km²

2. Method

The cytogenetics database at PathWest Laboratory was interrogated to identify patients diagnosed with CML from January 2017 to June 2021. Patients in this study were included based on a new diagnosis of CML since January 2017, with the presence of ACAs. Of 193 patients diagnosed with CML in this period, 14 presented with ACAs. The cytogenetics laboratory of PathWest covers all patients in Western Australia.

The cases were reviewed in conjunction with medical records from the associated hospitals and case files from the treating haematologists in Western Australia, which included care in the public and private systems. Similarly, results from private laboratories were also used regarding progress and response to therapy. Ancillary data from molecular laboratories were included.

Overall survival (OS) was calculated from date of diagnosis until death, and probability of OS was calculated using the Kaplan-Meier method [6].

Real-time quantitative PCR was performed according to Xpert BCR-ABL Ultra (Cepheid Innovation). Major molecular response (MMR) was achieved if the BCR-ABL/BCR ratio was <0.1% on the International Scale (IS) [7]. Cumulative incidence of MMR was calculated according to the Kaplan-Meier method [6].

Ethics approval for this study was obtained according to Fiona Stanley Hospital policy. Informed consent for research and publication was obtained from all participants.

3. Results

Of the 14 patients with ACAs, the average age at diagnosis was 59 years (range 35–89), 43% (n = 6) male, with an average presenting white cell count of 93 × 10⁹/L (range 4.4–739). One patient was previously treated for Hodgkin Lymphoma.

Detailed patient characteristics are presented in Table 1. All patients were treated with TKIs. Eight out of 14 (57%) were commenced on dasatinib, five on imatinib and one on nilotinib. No patients received ponatinib, bosutinib, or asciminib. Six patients were later changed to a second TKI (four to nilotinib, one to dasatinib, one to imatinib). Eleven presented in chronic phase; three patients presented in blast crisis and received concomitant chemotherapy. These three patients went onto allogeneic transplant. All are alive as of November 2021, although one has significant graft-versus-host disease. The third patient is progressing well at day +60 post-ASCT. No other patients have yet received transplants.

At average follow-up of 27 months, the overall survival is 86% (n = 12). One year after diagnosis, the mean qPCR (% IS) was 0.0609, corresponding to MMR. All patients with major breakpoints have qPCR <0.1% on current testing. Ten patients achieved MMR in the study period, with a median time to MMR of 3.5 months. Cumulative incidence of MMR was 0.769, and is presented in Fig. 1. Two 90-year-old patients died from respiratory infections – one with normal white cell count and the other in blast crisis. Kaplan-Meier analysis of overall survival is presented in Fig. 2.

The ACAs were very heterogeneous. Major-route abnormalities were present in 7 patients, the most frequent (n = 5) being additional chromosome 8 (+8), which was the sole additional abnormality in one patient. Two patients had ider(22)(q10)t(9;22); two patients had i(17q); one patient had trisomy 19.

Of 14 patients, 10 (71%) expressed major breakpoints, 2 (14%) expressed minor breakpoints and 2 (14%) micro breakpoints. Table 2 provides a comparison of molecular and cytogenetic data.

4. Discussion

The prognosis of CML patients has dramatically improved with the development of TKIs. The first TKI, imatinib, was approved in 2001 [8]. Since then, the second-generation (dasatinib, nilotinib and bosutinib) and third-generation (ponatinib, asciminib) TKIs have provided more potent alternatives, as structured in current guidelines [9]. In the pre-TKI era, median survival was 3–6 years; currently, patients generally have normal lifespan [8].

The appearance of additional cytogenetic abnormalities (ACAs) usually represents a mechanism for resistance to imatinib [8], and disease progression [10]. ACAs develop in 30% of accelerated phase (AP) patients, and in 80% of patients in blast crisis (BC) [2]. At diagnosis, however, ACAs occur in 5–10% of patients [2,10,11]. Consistent with this frequency, in our study, 7.3% of patients (14/193) diagnosed with CML from January 2017 to June 2021 presented with ACAs.

Detailed study of individual chromosomal abnormalities has informed risk-based classification systems for both myelodysplastic syndrome and acute myeloid leukaemia [12]. In CML, individual ACAs have not been extensively classified, but have been grouped into either ‘major route’ abnormalities (+8, +19, +pH, i(17q), ider(22)(q10)t(9;22)(q34;q11)) [8], or ‘minor route’ changes, comprising more heterogeneous abnormalities [12]. The major route abnormalities are more common and are present in >10% of patients with ACAs [12].

European LeukaemiaNet recommends that patients with major route ACAs should be classified as high risk, with minor route abnormalities yet to prove significant for progression [9]. This has been confirmed by studies of large cohorts of patients. MMR, defined as the presence of <0.1 BCR-ABL/BCR transcript ratio in peripheral blood, correlates with excellent progression-free survival [7]. The Italian GIMEMA Working Party on CML analysis group reported significantly inferior rates of MMR, and significantly longer time to reach MMR in patients with ACAs, compared to patients without [10]. The cumulative incidence of MMR was 0.67 and 0.89 in patients with and without ACAs, respectively [10].

The cumulative incidence of MMR in our cohort of patients with ACAs was 0.77.

Similar results were produced in a long-term observation of 1151 patients from the CML Study IV, where patients with major-route ACAs also had significantly inferior rates of overall (OS) and progression-free survival (PFS) [11]. Clark et al. [13] also found that patients with ACAs had significantly worse progression-free survival and freedom from progression compared to patients without ACAs.

Of the ACAs present in our study, major-route abnormalities (+8, 9

### Table 1

| Characteristic | Patients with ACAs (N = 14) |
|---------------|-------------------------------|
| Mean age at diagnosis, y (range) | 59.7 (35–89) |
| Sex, male/female, N (%) | 6/8 (43/47) |
| Mean Hb level, g/dL (range) | 107 (68–145) |
| Mean platelet count, 10⁹/L (range) | 361 (31–1035) |
| Mean white cells, 10⁹/L (range) | 93.2 (4.4–77.1) |
| Initial TKI, N (%): | 14 (100) |
| Dasatinib | 8 (57) |
| Imatinib | 5 (36) |
| Nilotinib | 1 (7) |
| Second TKI, N (%): | 6 (43) |
| Nilotinib | 4 (29) |
| Dasatinib | 1 (7) |
| Imatinib | 1 (7) |
| Additional chemotherapy, N (%) | 3 (21) |
| Allogeneic stem cell transplant, N (%) | 3 (21) |
| qPCR, mean (% IS) | 81.9 (35–89) |
| 3 months | 1.75 |
| 12 months | 0.0609 |
| Presence of major breakpoint, N (%) | 10 (71) |
| Presence of minor breakpoint, N (%) | 2 (14) |
| Presence of micro breakpoint, N (%) | 2 (14) |
| Alive, N (%) | 12 (86) |
| Mean follow-up, months | 27 |

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E. Leung et al.
+19, i(17q), ider(22)t(9;22)(q34;q11)) were present in 7 patients (4% of total patients; 50% of patients with ACAs). Of these 7 patients, one (who also had the e1a2 fusion transcript) died in May 2020. Another presented in blast crisis and received an allogeneic stem-cell transplant; qPCR performed at 12 months was 0.13.

Major-route abnormalities were present in 5 patients in the GIMEMA group (1.3% of total patients; 24% of patients with ACAs) [10], and in 16 patients in the CML Study IV (1.4% of total patients; 20% of patients with ACAs) [11].

In our cohort, trisomy 8 was the most frequent ACA, occurring in five patients. Trisomy 8 was the most common major-route ACA in studies from Germany [11] and Italy [10]. Anand et al. reported trisomy 8 and double Ph chromosome as the most common ACAs [14]; double Ph chromosome was the most frequent ACA in a study by Tashfeen et al. [2]. These studies all had large cohorts (range 208–1151 patients); however, there are only small sample sizes for patients with ACAs due to the rarity of these abnormalities. Interestingly, trisomy 8 may develop in Philadelphia-negative cells during imatinib treatment for CML; however, Kim et al. [15] concluded this to be a transient development and not related to therapy-related myelodysplasia or acute leukaemia.

In the vast majority of CML patients, the BCR gene breakpoint is found within the ‘major breakpoint cluster region’ (M-bcr), between exons e12-e16, encoding for a protein of 210 kD [16]. These fusion transcripts are either e13a2 or e14a2 junctions, and occur in around...
95% of CML patients [4,13]. Two other breakpoints are described: the minor breakpoint cluster region (m-bcr), with an e1a2 fusion transcript translating into a 190 kD protein; and the rare micro breakpoint cluster region (u-bcr), with an e19a2 transcript encoding for a 230 kD protein [16].

The e1a2 transcript is common in acute lymphoblastic leukaemia [17], but occurs in only 1–2% of CML patients [18,19]. Due to its rarity, there is limited data on its prognostic significance, with only small sample sizes; however, current literature suggests that patients with the e1a2 transcript are at high risk [20].

In analysis by Pardanani et al. [18], 3 patients were diagnosed with e1a2 transcripts out of 143 CML patients. Two of these were in chronic phase (CP) whilst one was in AP. The CP patients received imatinib as frontline therapy; complete haematological response (CHR) lasted less than two years. Both received salvage TKI, with the best response to dasatinib. The patient in AP received imatinib following interferon intolerance, and achieved complete cytogenetic response (CCyR). Verma et al. [20] identified fourteen patients with the e1a2 transcript, out of 1292 CML patients. Nine of these were in CP, of whom six received a TKI as frontline therapy. Cytogenetic responses were of short duration, and 5 of the 9 CP patients progressed to either AP or BC after a median of 48 months. A further study by Montoriol-Sabaté et al. demonstrated poor and short-lived responses to TKI therapy in four patients with the e1a2 transcript [21].

In keeping with such inferior outcomes, two out of 14 (14%) of our patients presented with the e1a2 fusion transcript. Both were diagnosed in CP with ACAs (as per Table 1). One of these patients was 89 years old at diagnosis. He received front-line dasatinib but switched to low-dose imatinib due to tolerability. He died 13 months after diagnosis of a respiratory infection with normal neutrophil counts.

The second patient had tolerance issues with psychological aspects, and has received three TKIs. At 12 months, her qPCR was 79.4% associated with poor compliance, which has subsequently improved. She continues on nilotinib with current qPCR of 2.44%.

Gong et al. [19] found that the e1a2 transcript is associated with increased incidence of ACAs at diagnosis. In our study, of the cohort of 193 patients, the only two patients with the e1a2 transcript also presented with ACAs at diagnosis. Due to the rarity of simultaneous minor breakpoint and ACAs at diagnosis, the degree of inferior prognostic significance is unclear; separately, however, each is a higher-risk factor.

Out of 193 CML patients in Western Australia during the time of our study, four (2%) have the e19a2 breakpoint; two of these were in the cohort of 14 with ACAs at diagnosis (Table 2). The e19a2 breakpoint has previously been reported as exceptionally rare, with Arun et al. [5] reporting a frequency of 0.3% (4/1260). The e19a2 breakpoint has also been described as neutrophilic-chronic myeloid leukaemia (CML-N), and was originally thought to have a more indolent course [20]. More recently, however, cases of e19a2-transcript patients with rapid progression to BC have been described [4,22]. Prognostic value of this extremely rare breakpoint therefore remains uncertain. Interestingly, of 23 e19a2 patients reported by Verstovsek et al. [22], 8 presented with ACAs.

The two patients in our cohort with the e19a2 transcript were diagnosed in 2019 and 2020, respectively, and are both receiving dasatinib. Neither has required secondary TKI. Both are alive, and have
experience no major complications as of October 2021. Further follow-up is required to see how these patients fare long-term; however, their current clinical picture is of an indolent course.

A limitation of our study is the size of our cohort; however, due to the rarity of additional cytogenetic abnormalities at diagnosis, large meta-analyses incorporating international data would be required to investigate the outcomes of these patients. Our cohort’s mean qPCR of the survivors at final follow up of 0.0609 corresponds to MRM, which is associated with improved prognosis [7]. Continued follow-up will be required to ascertain whether MMR is sustained, or CMR achieved. However, patients presenting with ACAs at diagnosis may be at a more advanced stage of disease, in that 3/14 presented in blast crisis in our study, which is associated with poorer outcomes.

The increasing understanding of CML, including additional cytogenetic abnormalities and mutations, and availability of newer treatments have improved outcomes in CML over several decades; this extends to the management of patients in our study.

5. Conclusions

Our study identifies high proportions of certain breakpoints and variable outcomes in newly diagnosed CML patients with additional chromosomal abnormalities in Western Australia. It adds to the available literature of the rare CML patients presenting with additional chromosomal abnormalities at diagnosis. Optimal management needs to be individualised and is evolving, including utilisation of newer therapies.

The varying patient factors including age and comorbidities need to be considered, together with the phase of CML at the time of diagnosis.

The biological factors associated with the cellular genetic information and mutational status may assist in guiding therapy. As illustrated in our cases, management may be dictated by current guidelines, such as younger patients presenting in blast crisis with ACAs proceeding to blast crisis in our cases, management may be dictated by current guidelines, such as younger patients presenting in blast crisis with new combinations of TKI, vigilant molecular monitoring and consideration of newer therapies and combinations.

Further scientific information, publications and guidelines for patients with additional cytogenetic abnormalities in CML promise to advance the great success in management of this disease.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

Many thanks to the clinical and laboratory staff at PathWest Laboratory Medicine and Fiona Stanley Hospital; to the clinical haematologists of Western Australia; to Dr Maryam Habibi for her invaluable contributions; and to the Royal College of Pathologists Australasia, the Government of Western Australia, and the University of WA for financial support.

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