Molecular responses in e19a2 BCR-ABL1 chronic myeloid leukemia

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The vast majority of chronic myeloid leukemia (CML) patients express either the e13a2 or e14a2 BCR-ABL1 oncogene fusion transcript with a recent international study showing that approximately 2% of patients express rare BCR-ABL1 fusion transcripts, usually as a result of alternative BCR or ABL1 exon splicing [1]. The most commonly reported BCR-ABL1 variant in CML is the e1a2 fusion with both a genotype-phenotype association and relatively poor responses to tyrosine kinase inhibitors (TKI) recognised [2]. The next most common variant BCR-ABL1 is the e19a2 fusion (encoding a p230 kDa oncoprotein) yet the overall TKI response of CML patients expressing this transcript is difficult to ascertain due to possible publication bias: most patients have been reported as single cases or small series presenting with atypical or novel aspects of morphology, cytogenetics or ABL1 kinase domain mutation status and have been treated with a variety of TKIs either as first- or second-line therapy. Furthermore, given the current possibility of treatment-free remission (TFR) in CML patients in long term deep molecular responses, there remains a lack of information on the feasibility of such an option in CML patients expressing e19a2 BCR-ABL1 transcripts.

To address the above concerns, the presenting features and molecular responses in a consecutive series of e19a2 BCR-ABL1 expressing patients referred for investigation at a de facto national CML molecular monitoring centre were considered. At the time of audit, 7/717 (1.0%) of Philadelphia chromosome-positive (myeloid leukemia patients undergoing molecular monitoring were identified as expressing e19a2 BCR-ABL1 transcripts (Table 1), confirmed at diagnosis in all cases by Sanger sequencing and with reverse transcription-quantitative PCR monitoring performed as previously described [3]. Median age of presentation was 66 years with molecular follow up ranging from none to more than ten years. Six patients had CML of whom five (83.3%) presented in chronic phase, one in accelerated phase (#7) with one further patient presenting as pH+ acute myeloid leukemia (#6). Significant comorbidities were present in the three patients older than 75 years at presentation (#2, #3 and #5) of whom two died within one year (#3 and #5). Of the three patients with a follow-up of more than one year (#1, #2 and #4) deep molecular responses beyond MR4 have been achieved.

The largest series of e19a2 BCR-ABL1 CML patients reported to date comprises of 33 chronic phase patients and of the sixteen who underwent molecular monitoring on frontline imatinib, complete cytogenetic response and major molecular remission rates were lower than in those CML patients expressing the common BCR-ABL1 transcripts [4]. This appears somewhat counterintuitive given the subtle differences in achieving molecular responses between e14a2 and e13a2 BCR-ABL1 and the relatively poor outcome of e1a2 BCR-ABL1: it could be extra-

### Table 1

Characteristics of e19a2 BCR-ABL1 myeloid leukemia patients.

| Patient | Sex | Age (years) | Phase at diagnosis | Treatment | Molecular follow-up (months) | ABL1 mutations | Best molecular response | Last molecular response | Current status |
|---------|-----|-------------|-------------------|-----------|-------------------------------|----------------|-----------------------|------------------------|---------------|
| #1 M    | 26  | CP          | NIL               |           |                               | ND at diagnosis | <0.001                | 78.4                   | Alive         |
| #2 M    | 80  | CP          | IM > NIL > IM > DAS | 93      |                               | ND at diagnosis | <0.001                | 24.5                   | Dead          |
| #3 M    | 78  | CP > BP     | IM > NIL          | 8        |                               | ND at diagnosis | 24.5                  | 24.5                   | Dead          |
| #4 F    | 53  | CP          | IM > NIL          | 98       | Q252H at BP                   | ND at diagnosis | 0.002                 | 0.002                  | Alive         |
| #5 F    | 90  | CP          | HU                | 0        |                               | ND at diagnosis | –                     | –                      | –             |
| #6 M    | 66  | AML         | DA + DAS          | 7        | ND at diagnosis               | ND at diagnosis | 0.66                  | 0.79                   | Dead          |
| #7 M    | 35  | AP          | DAS               | 5        |                               | ND at diagnosis | 1.09                  | 1.09                   | Alive         |

M: male; F: female; CP: chronic phase; BP: blast phase; AP: accelerated phase; AML: acute myeloid leukemia; NIL: nilotinib; IM: imatinib; DAS: dasatinib; HU: hydroxyurea; DA: daunorubicin and cytarabine; ND: not detected.

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polated that CML patients expressing longer BCR-ABL1 fusion transcripts might have superior molecular response rates with TKI therapy [5]. Acknowledging this smaller cohort size, immediately apparent differences between the two sets of patients are the median age of presentation (43 years versus 66 years) and presenting phase (16/16 chronic phase versus 5/7 chronic phase) possibly reflecting ethnic differences. Clinical management issues in our series of e19a2 BCR-ABL1 patients appear to be similar to those patients with e13/e14a2 BCR-ABL1 transcripts namely co-morbidities in elderly patients (requiring reduced TKI doses, TKI switching or intermittent discontinuations) and presentations in or transformations to advanced phases of CML.

Encouragingly, in those e19a2 BCR-ABL1, chronic phase CML patients who are able to tolerate long-term TKI therapy, we report for the first time achievement of deep and sustained molecular responses leading to the possibility of attempting TFR.

Compliance with ethical standards

Ethical approval: This study encompassed standard of care, routine, clinical monitoring and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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