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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 who 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 (*BCR-ABL1/ABL1*%)	Last molecular response (*BCR-ABL1/ABL1*%)	Current status
#1	M	26	CP	NIL	127	ND at diagnosis	<0.001	0.03	Alive
#2	M	80	CP	IM > NIL > IM > DAS	93	ND at diagnosis	<0.001	78.4	Dead
#3	M	78	CP > BP	IM > NIL	8	ND at diagnosis Q252H at BP	24.5	24.5	Dead
#4	F	53	CP	IM > NIL	98	ND at diagnosis	0.002	0.002	Alive
#5	F	90	CP	HU	0	ND at diagnosis	–	–	Dead
#6	M	66	AML	DA + DAS	7	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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