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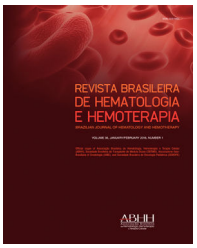

Letter to the Editor

Is karyotyping still needed in the diagnosis and monitoring of chronic myeloid leukemia?

Dear Editor,

We live in a digital era in which speed and knowledge turnover are very high. In this scenario, patients and physicians desire faster but precise diagnostic tests at a low cost.

Chronic myeloid leukemia (CML) is characterized by the presence of t(9;22)(q34.1;q11.2), the Philadelphia (Ph) chromosome, or the breakpoint cluster region-Abelson murine leukemia 1 (BCR-ABL1) rearrangement.[1] The diagnosis can be made using findings from peripheral blood (PB) exams combined with the detection of the Ph chromosome by karyotyping using a bone marrow (BM) sample or testing for the BCR-ABL1 by real time quantitative polymerase chain reaction (RqPCR) in PB or BM samples.

Comparing karyotyping with RqPCR, the former is a time consuming process that takes around 15 days while one gets the results of RqPCR in seven days. Furthermore, karyotyping is more expensive and performed after marrow aspiration whereas RqPCR may be carried out using PB. Therefore, some patients and doctors opt for the faster and cheaper test with easy sample collection and discard karyotyping.

However, both tests have their peculiarities and should be performed at diagnosis. Around 90% of CML patients have the classical Ph chromosome at diagnosis, but 5% may present variant translocations, involving chromosomes other than 9 and 22[2] that are usually not detrimental to tyrosine kinase inhibitor (TKI) therapy. Yet, the remaining 5% may have additional aberrations, also known as clonal evolution (CE), and these cases are associated with worse outcomes.[3–5] RqPCR does not detect these additional aberrations.

CE can be divided into major and minor routes. The major route (70% of cases) involves a second Ph chromosome (+Ph), +8, i(17q) or +19 or combinations. The minor route occurs in 30% of the cases and includes: −7, −17, +17, +21, −Y and t(3;21)(q26;q22). Recently, Wang et al.[5] showed that +8,−Y and +Ph have relatively good prognoses whereas the prognosis of patients with i(17)(q10), −7/del7q, and 3q26.2 are poor. Nevertheless, the European Leukemia Net and the World Health Organization (WHO)[1] guidelines consider the presence of the major route as accelerated phase disease whenever the abnormality was not present at diagnosis. Hence, the karyotype helps to define the disease phase.

Less than 2% of CML patients have normal karyotypes at diagnosis. In these patients, the BCR-ABL1 fusion gene can be detected by fluorescence *in situ* hybridization (FISH) or RqPCR proving that the use of karyotyping with one of these tests is valuable.

RqPCR, on the other hand, detects the BCR-ABL1 rearrangement in >95% of CML cases. The most frequent transcript types are b2a2 (e13a2) and b3a2 (e14a2) with the b2a2 type being associated with longer response time and lower response rates. Few patients present both types simultaneously.[6] The few BCR-ABL1 negative cases may have different breakpoints, not detected by regular primers used in the test. Here, the benefit of using both tests is once again clear. Those with a Ph chromosome positive karyotype, once sequenced have shown the BCR juxtaposed to ABL1 in exon 3.[7]

At diagnosis, the determination of transformation risk has an important role to establish the ideal therapy with appropriate doses and management. Pre-existing comorbidities may guide TKI selection. Patients who achieve complete cytogenetic remission may have life expectancy similar to the general population. Even so, a minority will progress to accelerated or blast phases.

According to the National Comprehensive Cancer Network (NCCN),[8] karyotyping is suggested at three and six months after starting TKI therapy to monitor therapy, if the RqPCR international scale (IS) is not available, at 12 months if complete cytogenetic remission (CCR) or major molecular response (MMR) is not achieved; or when there is one log increase in BCR-ABL1 transcript levels without MMR. Karyotyping performed in the course of the disease may reveal disease progression markers (CE). Moreover, in 5–10% of cases, karyotyping may show clonal alterations in Ph negative cells, which, in the absence of dysplasia, does not affect the outcome except for – 7/7q – that can evolve into myelodysplasia or acute leukemia and should be closely followed.[9]

RqPCR is much more sensitive than karyotyping and is thus indicated to detect progressive reductions in residual

transcripts. It is recommended to test every three months after starting TKI therapy until completing two years of complete cytogenetic response and every three to six months thereafter. In addition, in cases that lack ideal molecular response, the BCR-ABL1 mutation should be investigated and karyotyping performed in order to detect potential CE.

That said, karyotyping still has a relevant role in the diagnosis and monitoring of CML and should not be replaced by RqPCR, as the cheap alternative may turn out expensive in the end. The desire for a precise diagnosis, prognosis and choice of therapy does include karyotyping and RqPCR.

Conflicts of interest

The author declares no conflicts of interest.

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