SHORT COMMUNICATION

Fluctuation of *BCR-ABL1* qPCR^{IS} level beyond 0.1%^{IS} after stopping tyrosine kinase inhibitor in chronic myeloid leukaemia patients with deep molecular response for at least two years

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SUMMARY

Fluctuation of *BCR-ABL1* real-time quantitative polymerase chain reaction in International Scale (qPCR^{IS}) level below major molecular response (MMR) (0.1%^{IS}) is a known phenomenon after stopping tyrosine kinase inhibitor (TKI) in chronic myeloid leukaemia (CML) patients who are attempting treatment free remission (TFR). We report here four cases of fluctuation beyond MMR during conduct of a Malaysia Stop TKI Trial (MSIT) to examine the validity of the commonly used relapse criterion – loss of MMR for one reading – aiming to provide evidence in setting relapse criteria for future CML patients who want to attempt TFR.

KEYWORDS:
chronic myeloid leukemia, treatment free remission, BCR-ABL1, tyrosine kinase inhibitor, major molecular response

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that originates from an abnormal pluripotent bone marrow stem cell and is consistently associated with *BCR-ABL1* fusion gene[1], which can be quantitated using real-time quantitative polymerase chain reaction (qPCR) and standardized using International Scale (IS) (qPCR^{IS}).[2] One of the many advancements in the field of CML is the concept of treatment free remission (TFR), arguing the necessity of life long tyrosine kinase inhibitor (TKI). About 40% of CML patients, who had achieved deep molecular response (DMR) (molecular response (MR) of 4-log reduction (MR4) (0.01%^{IS}) or deeper) for at least two years, were able to stop TKI safely and remain in TFR, while 60% relapsed molecularly.[3-6] Criteria of relapse used in majority of stopping TKI trials are loss of major molecular response (MMR) (0.1%^{IS}) for one reading.[7,8] Fluctuation of qPCR level below MMR (0.1%^{IS}) is a known phenomenon after stopping TKI[4], probably due to interplay between the persistence of leukaemic stem cells and immunosurveillance.[8] To our knowledge, there no detail report on fluctuation that exceeding MMR, which is probably the reason it is recommended as a criterion of relapse[9] and used in most of the stop TKI trials.[7,8] During the conduct of Malaysia Stop TKI Trial (MSIT), we observed fluctuation of qPCR^{IS} levels beyond MMR that we feel think it is worth reporting to define safe and practical relapse criteria in CML patients who attempt TFR. Four cases of fluctuation exceeding MMR here.

MATERIALS AND METHODS

MSIT (Malaysia National Medical Research Register (NMRR): NMRR-13-1186-15491; ClinicalTrials.gov: NCT02381379) is a multi-center trial in Malaysia aiming to compare the outcomes of peginterferon (pegIFN)-α-2a for a year followed by observation versus observation after stopping TKI in CML patients with DMR for two years or more. Relapse was defined as: 1) one reading of loss of MMR (0.1%^{IS}), or 2) positivity of *BCR-ABL1* transcripts in qPCR^{IS}, as confirmed by a second analysis point, indicating the increase (≥ 1 log) in relation to the first analysis point at two successive assessments. The qPCR^{IS} test was sent monthly for the first 12 months, 2-monthly for subsequent 12 months, and 3-monthly thereafter and done in a central laboratory.

RESULTS

Two patients (P1 and P2) in the observation arm, both from the same study site (Sultanah Aminah Hospital) relapsed according to the relapse criteria no.1, i.e. loss of MMR (see Table I). TKI was reinitiated as per protocol. However, a repeated qPCR^{IS}, which was not prohibited in the study protocol, was done prior to the initiation of TKI, which showed DMR. Investigations showed no evidence of wrong sampling or laboratory error. After discussion, investigators decided to stop their TKI after two months of TKI intake.

These two "relapse" cases challenge MMR as a relapse criterion and raise doubt on the four relapse cases (R1 to R4, see Table I) prior to the incidence. We re-examined these four cases and could only truly confirm relapse in one case, in which the previous two successive readings showed 1-log increment, fulfilled our trial relapse criterion no.2, before loss of MMR.

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