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LETTER TO THE EDITOR

The magnitude of tyrosine kinase inhibitor induced cytopaenia on normal haematopoietic tissues in chronic myeloid leukaemia patients

Jew Win Kuan ✉, Si Yuan Ng, Siong Leng Hon, Soo Min Lim, Alvin Jung Mau Chai, Hock Gin Teo, Kar Ying Yong, Andy Sing Ong Tang, Su Kien Chiang, Gilbert Wilfred

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LETTER TO THE EDITOR

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Dear Editors,

At diagnosis of chronic myeloid leukaemia (CML), when most patients present at chronic phase, total white cell count (TWC) is typically high with variable haemoglobin (Hb) and platelet count (PLT), that is, low, normal and high—89.7%, 10.3% and 0% for Hb, respectively, and 7%, 22.5% and 70.4% for PLT, respectively.[1] Following commencement of tyrosine kinase inhibitor (TKI), which is the main treatment modality for CML in chronic (CP) and accelerated phase, cytopaenia or worsening cytopaenia occurs commonly during the first few weeks or months.[2] However, full blood count (FBC) would gradually normalize when the suppressed normal haematopoietic tissues gradually repopulate the bone marrow after TKI eliminates the CML leukaemic cell clone.

In the past, TKI is recommended for lifelong. With introduction of treatment free remission (TFR) concept,[3] CML patients with deep molecular response (DMR) for adequate duration are able to attempt to stop TKI. During conduct of our stop TKI study (Malaysia Stop TKI Trial [MSIT]),[4] as an out of planned finding, we observed a substantial increment of Hb, TWC and PLT after stopping TKI even though FBC were within normal range before stopping TKI. We think it is worthwhile to report the magnitude of the increment, which was not possible when TKI was and still is recommended for lifelong for majority of CML patients, because it reflects the magnitude of the TKI-induced cytopaenia on the normal haematopoietic tissue and guides physicians in treating CML patients with concomitant diseases, for example ischaemic heart disease that require higher level of Hb, to pursue on an attempt to stop TKI when permissible.

The methodology of MSIT was as described[4] with FBC as one of the monitoring tests during every visit. In brief, CML patients diagnosed in CP and in DMR for 2 years or more were randomized to either peginterferon (pegIFN)-α-2a for a year followed by observation or observation after stopping TKI (Malaysia National Medical Research Register [NMRR]: NMRR-13-1186-15 491; ClinicalTrials.gov: NCT02381379). The primary outcome was molecular relapse. The visit/monitoring was scheduled at monthly for the first 12 months, 2-monthly for subsequent 12 months, and 3-monthly thereafter.

A total of 30 patients were enrolled between July 2015 and October 2018 (pegIFN-α-2a arm $n = 15$, observation arm $n = 15$). All the patients were on imatinib, except one (designated as P23 in tables) on nilotinib. Up to October 2020, the number of relapses was 4 and 6 in pegIFN and observation arm, respectively. After excluding three patients with "false" relapse before Visit 18 (24 months after stopping TKI)[4] (P6, P13 and P14), one 83-year-old man who passed away 1½ months after stopping TKI due to cause unrelated to CML or stopping TKI (P30), and one 58-year-old lady withdrew from the study at Visit 3 (3 months after stopping TKI) due to severe TKI withdrawal syndrome in observation arm (P7), the 24-month trend (Visit 1 to 18) of Hb, TWC, and PLT of 11 and 6 non-relapse patients in pegIFN and observation arm, respectively, were studied (Figure 1A).

In observation arm ($n = 14$), mean (*SD*) magnitude of Hb, TWC, and PLT increment were 1.5 g/dl (0.6), 2.1×10^9/L (1.6), and 42.5×10^9/L (42.1) ($p \leq .002$), respectively (Table 1). The magnitude of increment was correlated and inversely correlated with age for Hb ($r = .36$) and PLT ($r = -.43$), respective, while no age correlation was found for TWC ($r = -.08$) (Figure S1a).

In pegIFN arm (Figure 1A), there was an increment in Hb and TWC after pegIFN was completed at Visit 12. Subsequently, all patients in pegIFN arm who have FBC data as minimum as Visit 14 were included for further analysis ($n = 14$) (Table 1) (P29 was excluded because she relapsed earlier than Visit 14). The increment were 1.3 g/dl (1.1) ($p = .001$), 1.7×10^9/L (1.4) ($p = .001$), and 19×10^9/L (51.1) ($p = .183$) in pegIFN arm ($n = 15$) after pegIFN was completed (not seen for nilotinib). The magnitude of Hb increment was correlated with age after excluded the outlier (P17, age 24) ($r = .33$), same as observation arm (Figure S1b). Interestingly, the inversion correlation between magnitude of PLT increment and age in observation arm was reversed in pegIFN arm ($r = .32$) and a marginal correlation was also found in TWC ($r = .30$) (Figure S1b).

The magnitude of the TKI-induced cytopaenia on the normal haematopoietic tissue was also evidenced from the FBC changes after restarting TKI in relapse patients (Figure 1B and Table 2). The mean (*SD*) magnitude of Hb and TWC decrement was 1.6 g/dl (1.1) ($p = .002$) and 2.1×10^9/L (1.8) ($p = .006$), respectively, while PLT did not show insignificant decrement, 3×10^9/L (54.0) ($p = .852$).

The magnitude of the TKI-induced cytopaenia on the normal haematopoietic tissue, lastly, was evidenced in the trend of FBC changes of four 'false' relapse patients,[4] in whom TKI was restarted for 2 months and re-stopped (Table SI).

