A RANDOMIZED CONTROL TRIAL COMPARING PEGINTERFERON-α-2a VERSUS OBSERVATION AFTER STOPPING TYROSINE KINASE INHIBITOR IN CHRONIC MYELOID LEUKEMIA WITH DEEP MOLECULAR RESPONSE FOR AT LEAST TWO YEARS

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Background:
There is much advancement in treatment of chronic myeloid leukemia (CML) since the approval of first tyrosine kinase inhibitor (TKI), imatinib, by US FDA in 2001. One of them is definitely the concept of stopping TKI, starting at the CML patients who have achieved deep molecular response (MR) of MR4.5 for a reasonable long period of at least two years, pioneered by the researchers from French and Australia. Meanwhile, interferon, the standard treatment of CML before the era of TKI, showed that interferon-responded patients may indeed retain the response once interferon was withdrawn via interferon-induced immunity towards the leukemic clone. This is further supported by stop trial in Japan, in which after stopping TKI, interferon was given for 2 years and it showed a higher drug-free rate compared to stop trial from French and Australia. Hence, it is logical to postulate the use of interferon after TKI was stopped when patients have attained deep MR for more than two years will increase the percentage of patients remain TKI-free on follow-up.

Materials and Methods:
This is a multi-center randomized controlled trial. Adult CML patients, diagnosed in chronic phase, treated with ongoing TKI for at least 3 years without previous history of TKI failure and have achieved stable deep MR on International Scale for ≥2 years with at least 2 readings of MR4.5 (including the latest before study entry), were randomized into 2 arms: (1) peginterferon-α-2a, subcutaneous weekly, starting at 180 mcg, or (2) observation. Disease is monitored by PCR (centralized in Ampang Hospital) at monthly for the first year, 2 monthly for the second year and 3 monthly for the third year. Relapse is defined as either (i) one reading of loss of major MR, i.e. reading of >0.1% IS and confirmed by second analysis taken 1 month later if the first analysis point reading is ≤1% IS, or (ii) positivity of BCR-ABL1 transcripts, as confirmed by a second analysis point, indicating the increase (at least 1 log) in relation to the first analysis point at two successive assessments. Quality of Life is assessed using EORTC QLO-C30.

Results:
At the time of writing, total of 8 patients were randomized, 5 into peginterferon arm, 3 into observation arm, all were on imatinib, M:F = 4:4, Malay: Chinese:Indian = 3:4:1, median age 49.5 (range 25-58), median follow-up 4 months (range 1-6) and none of them relapse. Two patients developed imatinib withdrawal syndrome, both female on observation arm, one was mild and resolved after 2 months but one was severe and needed termination after 2 months and restarted on imatinib. Two patients in peginterferon arm developed mild hepatitis with liver enzymes <2x of ULN. Four patients were able to tolerate peginterferon-α-2a at the dose of 180 mcg weekly, while one patient needed dose reduction to 90 mcg weekly. Quality of life score comparing two months after stopping TKI and baseline will be presented in the conference later.

Conclusion:
No conclusive date can be drawn so far because sample size is small and follow-up is short. Nonetheless, this trial provides Malaysian CML a platform to stop TKI safely.

Keywords: CML, peginterferon, stop, BCR-ABL