Supplementary Data

Contents

Randomization process and allocation concealment

The random allocation sequence with block was generated by biostatistician using Stata Intercooled software version 11.1. The block number was concealed to all except the biostatistician. The information of the allocated treatment was written down and concealed in a sealed opaque sequentially numbered envelope prepared by the biostatistician and kept by a research officer (RO) in-charge in the chief study center, Ampang Hospital. Each study patient was given a unique patient number by the RO according to chronological order of enrolment into the study. The RO opened the envelope with the sequential number matching the unique patient number and arranged the appropriate intervention and related procedures according to the information stated in the envelope.

PegIFN-α-2a

PegIFN-α-2a (PEGASYS®, F. Hoffmann-La Roche Ltd, Basel) was supplied as a sterile, single use, ready-to-use liquid for subcutaneous injection in the form of pre-filled syringes containing 0.5 mL of 180 µg pegIFN-α-2a. After education and supervision, it was self-

injected by patients subcutaneously at the starting dose of 180 µg weekly. Dose reduction to 135µg, 90µg, 45µg or stop was done according to protocol in case of side effects. If a female patient receiving pegIFN was pregnant, pegIFN would be withhold immediately and changed to subcutaneous conventional IFN-α-2a 3 MIU 3x per week.

Exclusion criteria

1) previous history of any TKI failure according to European LeukemiaNet 2009 (Baccarani, M., et al. (2009). "Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet." J Clin Oncol 27(35): 6041-6051.),

2) previous history of successfully engrafted autologous or allogenic HSCT and no relapse (as defined by protocol, see below) post-HSCT,

3) planned for autologous or allogeneic HSCT,

4) previous history of achieved CCyR with IFN/pegIFN,

5) had undergone or on immune-modulatory treatments other than IFN/pegIFN,

6) undergoing treatment for other malignancies,

7) hemoglobin < 9 g/dL and platelet count < 90 x 10^9/L for two successive readings of one month apart,

8) positive Hepatitis B surface Antigen (HBsAg), Hepatitis C antibody (anti-HCV), or Human Immunodeficiency Virus antibody (anti-HIV),

9) creatinine clearance of ≤ 50 mL/min,

10) persistent alanine transaminase (ALT) ≥ 2x upper limit of normal (ULN) for two successive readings of one month apart,

10) under law protection or without ability to consent,

11) previous history or on-going psychiatric illness, and

12) unable to come regularly for study procedures.

Peripheral blood for qPCR^{IS} for *BCR-ABL1* test

In brief, total ribonucleic acid (RNA) was extracted from a minimal 15 mL whole blood collected in tubes containing ethylenediaminetetraacetic acid. RNA (~1 µg) was subjected to one-step reverse transcription and qPCR using commercial kit (MolecularMD BCR–ABL1IS MR3 Assay™). Fusion (*BCR-ABL1*) and control (*ABL1*) gene transcripts were amplified in separate reactions and two replicates for each sample. Percentage of *BCR-ABL1*:*ABL1* ratio was calculated, then multiplied by a correction factor specified in the kit to obtain the percentage in IS.

Data collection, monitoring and safety precautions

The compulsory baseline investigations needed for enrollment were full blood count (FBC), liver function test, renal profile, fasting blood sugar, fasting lipid profile, HBsAg, anti-HCV, anti-HIV, thyroid stimulating hormone and electrocardiogram. The compulsory investigations during each scheduled visit were FBC and qPCR^{IS}. If patients were on pegIFN arm, the additional compulsory investigations were LFT and RP during each scheduled visit and TSH at least every 3-monthly for the first year.

The QoL assessment was performed at baseline, after stopping TKI for two months and one, two and three years using European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) version 3.

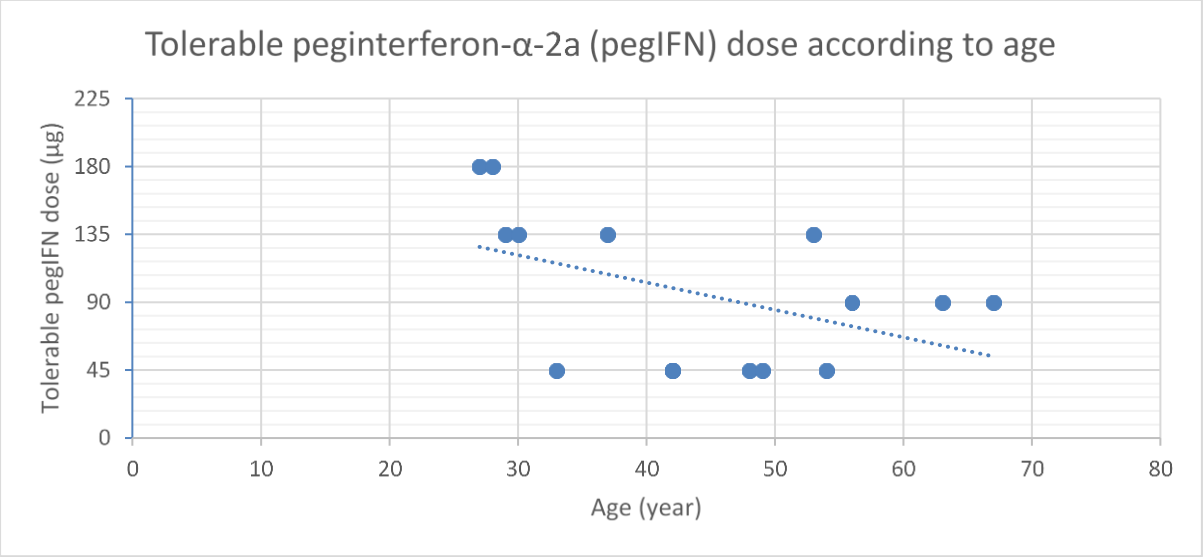
Withdrawal from study and death

[1]A patient, 58-year-old Indian lady, was withdrawn from the study after stopping TKI for three months due to severe TKI withdrawal syndrome not responding to nonsteroidal anti-inflammatory drug and steroid.

[2] A patient, 83-year-old Iban gentleman, passed away after stopping TKI for one and a half months due to acute abdomen, secondary to ischaemic bowel with underlying coeliac

artery aneurysm and extensive atherosclerosis from aortic arch until bilateral common iliac arteries, leading to sepsis, complicated by acute on chronic kidney failure. He was also known to have congestive heart failure and history of admission due to ischaemic bowel. The computed tomography of thoracic and abdominal aorta seven months before starting intervention showed celiac artery aneurysm, focal aneurysm at the root of right main renal artery, ascending aorta aneurysm and unilateral left renal artery stenosis. We do not think the cause of death was due to CML or TKI withdrawal.

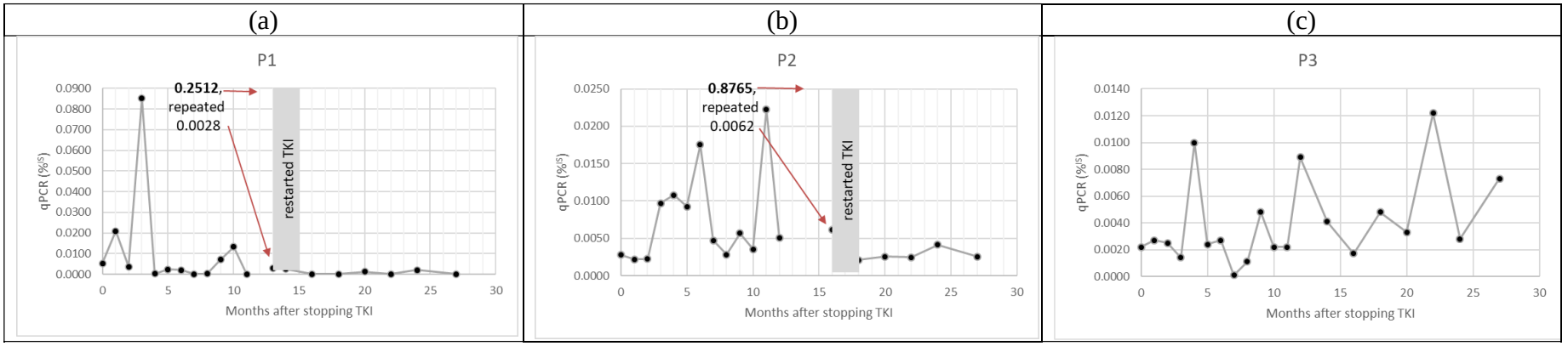
Supplementary Figure 1



Supplementary Figure 1. Tolerable peginterferon-α-2a dose in 15 patients

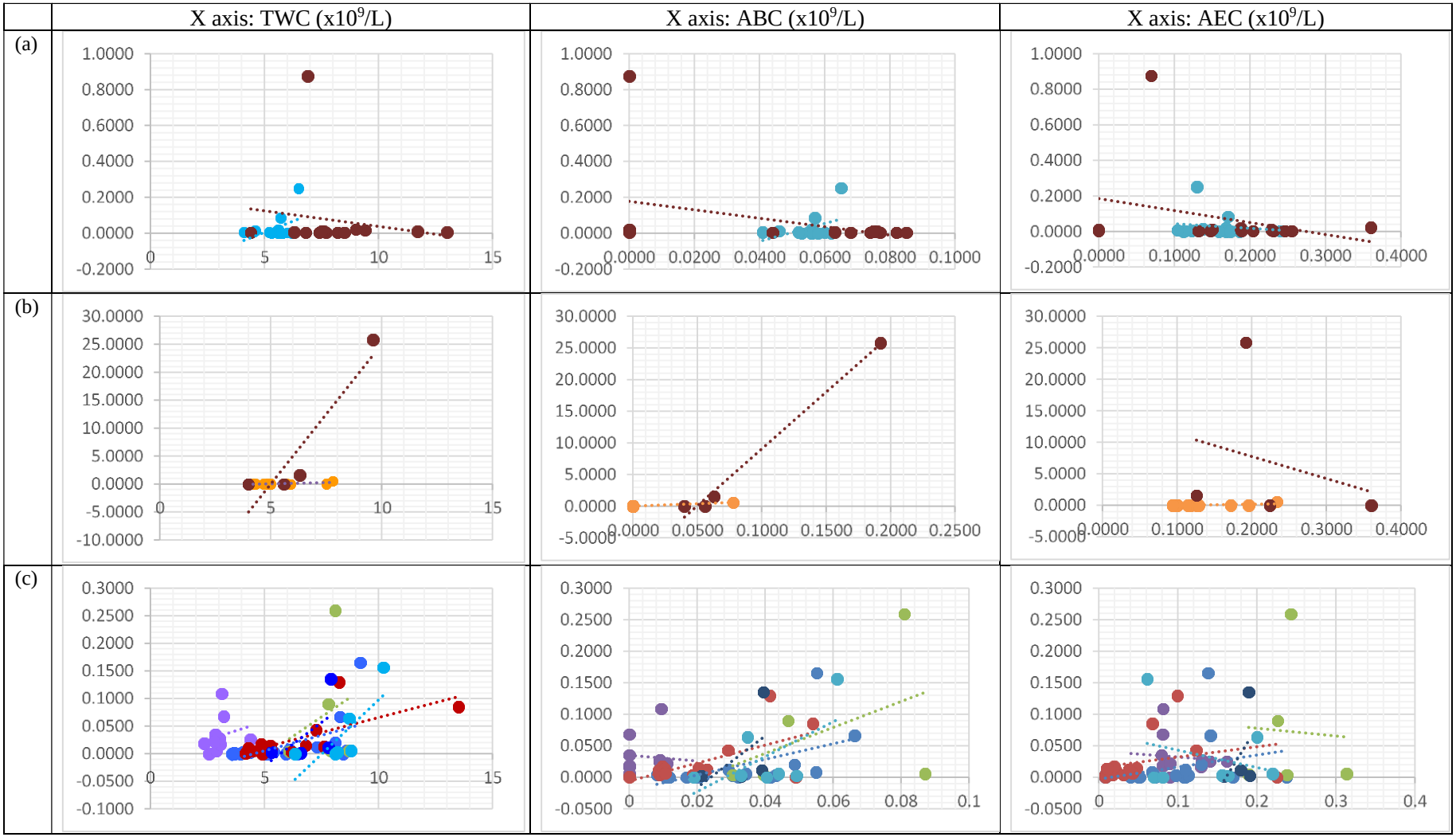
Supplementary Figure 2

Month after stopping TKI		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	16	18	20	22	24	27
qPCR ($\%^{IS}$)	**P1**	0.0053	0.0209	0.0036	0.0851	0.0002	0.0023	0.0020	0.0001	0.0003	0.0070	0.0133	0.0001	**0.2512**	0.0028	0.0026	0.0001	0.0001	0.0011	0.0001	0.0020	0.0001
	P2	0.0028	0.0022	0.0022	0.0097	0.0108	0.0093	0.0175	0.0047	0.0028	0.0057	0.0035	0.0222	0.0051	-	**0.8765**	0.0062	0.0021	0.0026	0.0025	0.0041	0.0026
	P3	0.0022	0.0027	0.0025	0.0014	0.0100	0.0024	0.0027	0.0001	0.0011	0.0048	0.0022	0.0022	0.0089		0.0041	0.0017	0.0048	0.0033	0.0122	0.0028	0.0073



Supplementary Figure 2. (a) The trend of real-time quantitative polymerase chain reaction in International Scale ($qPCR^{IS}$) in the two fluctuation cases (P1 & P2) and a representative patient (P3) with fluctuation of $qPCR^{IS}$ (grey-filled box indicates tyrosine kinase inhibitor (TKI) was restarted)

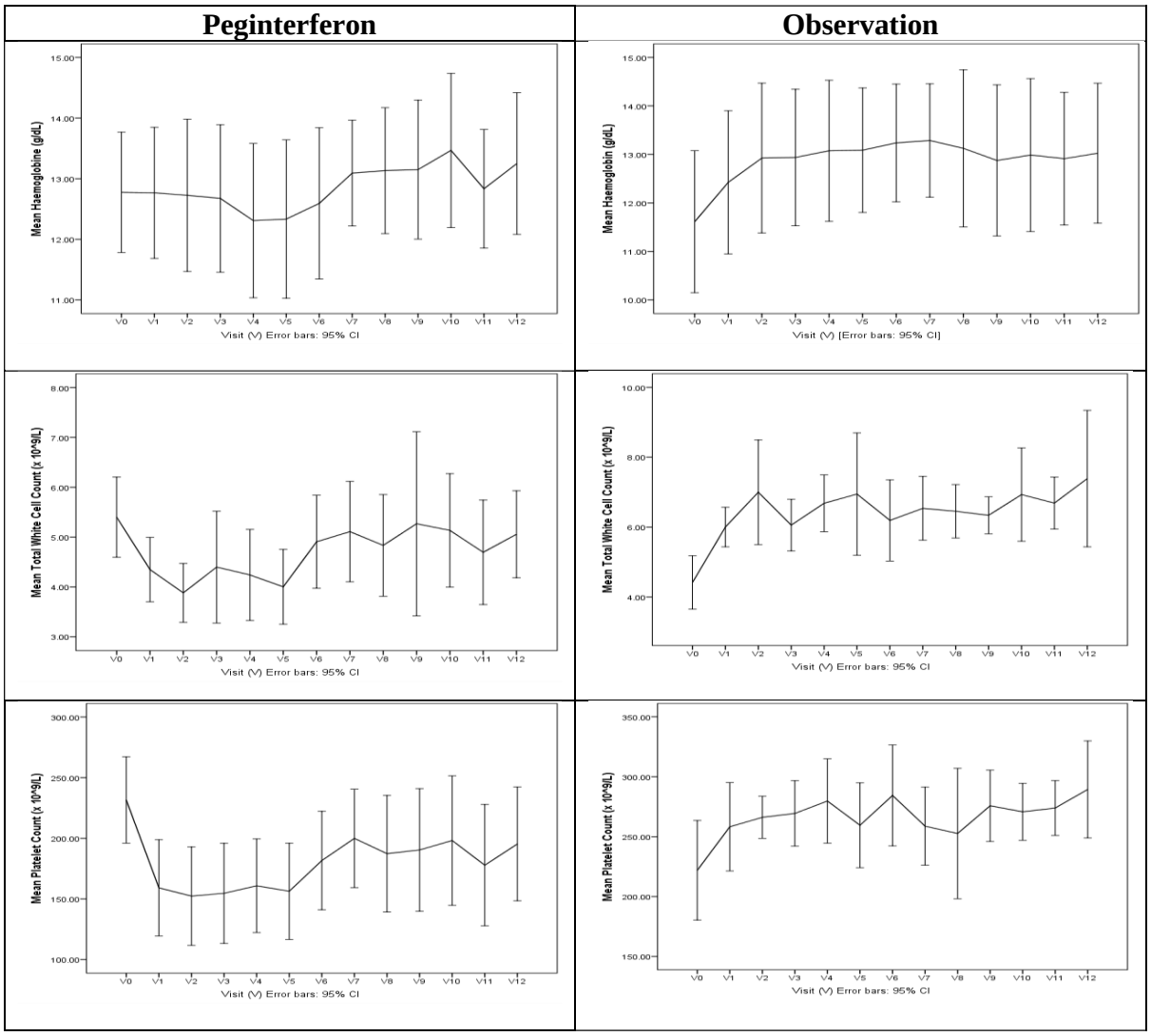
Supplementary Figure 3



The blood count data in Supplementary Figure 3 (a) and (b) was not combined with other study sites because this study site reported percentage of basophil and eosinophil as whole number, while the other study sites reported in one decimal point.

Supplementary Figure 3. (a) the association between total white cell count (TWC), absolute basophil count (ABC) and absolute eosinophil count (AEC) and quantitative real-time polymerase chain reaction in International Scale ($qPCR^{IS}$) in the two fluctuation cases, (b) the association between TWC, ABC and AEC and $qPCR^{IS}$ in the two relapse patients from the same study site as in the two fluctuation cases, (c) the association between TWC, ABC and AEC and $qPCR^{IS}$ in the other relapse patients from other study sites. All Y axis: qPCR ($\%^{IS}$)

Supplementary Figure 4



Supplementary Figure 4. The trend of haemoglobin, total white cell count and platelet count after stopping tyrosine kinase inhibitor (TKI) during monthly visit in the first year. The data after restarting TKI is not included in the analysis.