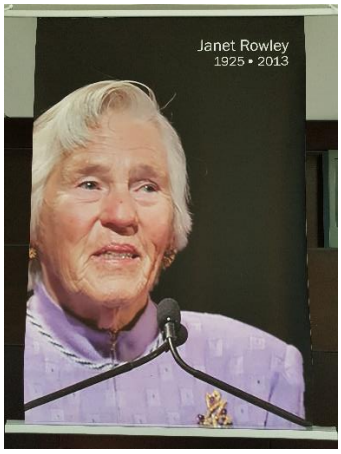
Report of John Goldman Conference 2019

September 12-15, 2019

Palais des Congrès de Bordeaux, Bordeaux, France

In remembrance of Dr John Goldman (1938 - 2013) and Janet Rowley (1925 - 2013) for their contribution in the field of CML. In remembrance of Dr Visalachy Purushothaman (1947-2019), who has inspired me to be a haemotologist and who I am today, for her contribution in the development of Haematology subspecialty in Malaysia.



Thursday, September 12, 2019

Dr Francois-Xavier Mahon gave a welcome talk that began the conference. It was informative. I got to know that John Goldman Conference (JGC) was 1st organized in 2008. The 2nd JGC was organized in Bordeaux in 2009. So, this year's JGC is back to Bordeaux after 20 years. This year's JGC is also the 1st time co-organized together with International Chronic Myeloid Leukemia (CML) Foundation.

In today's agenda, my initial highlight was Dr Susan Branford's presentation – "An RNA-based multi-gene next generation sequencing (NGS) technique detects more cancer gene mutations than a DNA-based method for the assessment of patients with CML" because it was related to my research. It is one of the four top scoring abstracts of the conference. The authors of the top scoring abstracts were awarded with certificate and full sponsorship for next year's JGC. Dr Susan Branford presented her study well and clearly. Her study used FreeBayes variant caller which consisted of 126 genes. However, I could not conclude that the RNA-based multigene NGS is a better approach than Whole Exome Sequencing (WES) in my study. I think it is still better to use WES if no previous data on a studied cohort.

I like Dr Michael Deininger's lecture – "Are we done or are we stuck? Frontiers in Chronic Myeloid Leukemia". He received this year's Janet Rowley Award. Management of CML has progressed so much since the discovery of Philadelphia chromosome in 1960. The disease prognosis has changed from a doom disease to a disease that most patients have a near normal life span. Are we done or are we stuck? What else do we want to achieve? What direction of CML should we go from there? Researches and grants for CML are declining compared to, for example, acute myeloid leukemia, which is increasing. Dr Michael Deininger shared his thoughts, perhaps we should re-think some of our approaches, for example, looking at BCR-ABL1 transcript types and CML outcomes, not getting

too obsessed the biological differences between BCR-ABL1 kinase domain mutants, questioning whether is everything knowable worth knowing by giving example of propofol enhances BCR-ABL tyrosine kinase inhibitors (TKIs)' inhibitory effects in CML through Akt/m TOR suppression and there are a lot that we still do not understand about BCR-ABL1 independence. He also pointed out some really tough challenges in treatment free remission (TFR) – will we ever be able to predict success? How many attempts until it's time to give up? Why is it not a reality for many more patients? One thing that he mentioned that alert me to continue be vigilance in our Malaysia Stop TKI Trial (MSIT) patients is the non-plateauing TFR curve in EURO-SKI; we have to continue monitoring the patients who have not relapse after stopping TKI for a year and above. From the extrapolation of the curve, it seems that all patients who stop TKI will eventually relapse after 15 years. We should find the weak spot in CML stem cells. The last three questions we should look out: is CML incidence rising? Low use of TKIs in patients more than 65 years old and some parts of the world that are still far behind in CML management.

Another top scoring abstract that caught my attention is Dr. Giora Sharf's study – "TFR4CML – Understanding the perspective of CML patients on stopping treatment". It was an online survey that recruited 1016 patients from 68 countries. The result that alerted me was from the patients who had to restart treatment, 91% felt disappointed and 59% scared and depressed. Higher proportion of female patients reported feeling worse both physically and emotionally after restarting treatment than before stopping. It reminded me to spend more time for one of my MSIT patients during the next visit and to share this info with all the other co-investigators.

Friday, September 13, 2019

My highlight of the day is Dr. Jeff Miller's lecture – "Novel ways to activate and target NK cells with specificity to leukemia: from individual to off-the-shelf products". Natural killer (NK) cells are important for CML control. The conclusive message that I received is autologous NK cells, harvested from peripheral blood (PB), is not working. Allogenic NK cells should be used. Expansion and persistence of donor NK cells in vivo using IL-15 is better than IL-2 because unlike IL-2, IL-5 does not stimulate Treg that express IL-2Rα (CD25), but I did not hear comment on the comparison between IL-15 and IL-2 diphtheria toxin fusion protein (IL-2 DP); IL-2 DP is hypothesized to be able to eliminated host Treg and enhance in vivo expansion of donor NK cells. Preliminary test using monomeric rhIL-15 given subcutaneously and weekly seemed to improve overall survival in refractory acute myeloid leukemia (AML). Investigators are heading into new studies using monthly injection. Another approach that was discussed is using adaptive NK cells that have better function and persistence. On top of the adaptive NK cells, further modification of the NK cells mimicking the concept of chimeric antigen receptor T cells (CAR-T) might be applicable to NK cell therapy. Besides that, using the concept of bispecific T engager (BiTE)-mediated killing, e.g. blinatumomab (anti-CD19 and anti-CD3), a bispecific NK engager (BiKE) (anti-CD16 and anti-CD33) or trispecific T engager (TriKE) (anti-CD16, anti-CD33 and hIL-15) would be an interesting idea. In fact, Dr. Jeff said TriKE was approved by FDA and expected to dose first AML patient soon. Dr Jeff also mentioned about using induced pluripotent stem cells (iPSC) to produce induce NK cells. In fact, the study using iPSC has started in advanced solid tumour in United State. Applying the above in CML, we might be able to increase TFR by using IL-15, IL-15 TriKE and IL-15 tethered off-the-shelf NK cells.

Another interesting thing that I learnt from Dr. Oliver Hantschel's abstract presentation –" Integrative phosphoproteome and interactome analysis identifies Sts-1 (UBASH3B) phosphatase as a tumor suppressor and possible therapeutic target in CML and Ph+-ALL". Sts-1 (UBASH3B) is a novel BCR-ABL interactor, the 7th found after Grb2, Crk, Shc, p85, Cbl and SHIP-2.

Saturday, September 14, 2019

My highlight of the day is "TKI resistance in CML: is it all about mutations?" by Dr. Michael Deininger. The answer to the lecture's title is, of course, no. Mechanism of TKI resistance can be divided into BCR-ABL dependent or independent. BCR-ABL dependent resistance is, exemplified by the ATP-site point mutation, like T315I. Developing a more potent TKI to overcome certain point mutation is a never-ending battle because resistant clones to the more potent TKI will eventually emerge. A new drug, asciminib (ABL001), that reduce BCR-ABL degradation by fitting into myristoyl Pocket of BCR-ABL, might be able to help that. Data of asciminib was presented in three abstract presentations – "Two stones for one bird: combining asciminib and ponatinib to target clinically problematic BCR-ABL1 compound mutants" by Dr Thomas O'Hare (BCR-ABL1 compound mutants mean presence of more than one mutation in a CML clone c.f. BCR-ABL1 polyclonal mutations), "Combination of asciminib+imatinib in previously treated CML patients: phase 1 study results" by Dr Tim P. Hughes and "Combination of asciminib+nilotinib or asciminib+dasatinib in previously treated CML patients: phase 1 study results" by Dr Delphine Réa. I have not use asciminib, but again, the never-ending battle, I anticipate asciminib is not the answer. Escape from the asciminib can be easily done by mutation in myristoyl site. BCR-ABL1 independent resistance can be further classified into kinase independence, e.g. adhesion defect and migration defect, and complete independence, that can be further classify into extrinsic and intrinsic. BCR-ABL1 dependence is probably less important than independence in minimal residual disease (MRD) state and blast crisis phase of CML than in chronic phase.

The never-ending battle is not only in BCR-ABL1 TKI, but also in FLT3 inhibitor, presented by Neil Shah in his lecture "Mechanisms of resistance to FLT3 inhibitors and how to overcome them" and CAR-T, presented by Dr Andrei Thomas-Tikhonenko in his lecture "How lymphoid malignancies escape CART cells". The moral of the conference that I learnt is you will never ever eliminate all bad guys. We will only be exhausted at the end chasing the tail of the bad things. Perhaps the most strategic tactic is still the public health's principle – identifying the risk factors (in CML, probably understanding more of the critical events of leukemogenesis) and screening and detection of the disease at its earliest phase (in CML, targeting the leukemic stem cell. Can we use BCR-ABL1 to screen?), which are addressed in some abstract presentations.

Sunday, September 15, 2019

I attended WORKSHOP FOR NON-CLINICAL SCIENTISTS #2: ROLE OF INFLAMMATION IN CML/MPNs. It is very interesting. Interferon was discussed in two lectures – "Homeostatic interferon priming in haematopoietic stem cells" by Dr Marieke Essers and "The role of interferon and other inflammatory cytokines in the pathogenesis and treatment of CML/MPN" by Dr Steffen Koschmieder. "Gli1 and stromal cells in MPN" by Dr Rebekka Schneider-Kramann illustrated Gli1+ cells proliferate and migrate, then differentiate into myofibroblasts that produces the extracellular matrix in myelofibrosis. CXCL4 ameliorates the MPN phenotype, reduces Gli1+ cell activation, reduces JAK/STAT activation in megakaryocytes and stromal cells and reduces inflammation in stromal cells. Hence, CXCL4 might be a therapeutic target. Between mesenchymal cell (MSC) type 1, 2, 3 and 4, MSC type 1 and 2 are more implicated in pre-fibrosis phase. IL-33 is important due to its effect to MSC, but the effect is not clear yet because IL-33 has anti-fibrotic and pro-inflammatory effect on MSC. Plasma S100A8 could be a marker that can be used to mark the onset/progression of fibrosis. However, upon my inquiry, Dr Rebekka has not correlate plasma S100A8 with lactate dehydrogenase (LDH), which is easily available for clinical practice in monitoring polycythaemia vera and essential thrombocythaemia transformation into secondary myelofibrosis. Dr Tim Brümmendorf, chairperson

of the workshop, added that plasma S100A8, and of course LDH, might be also a marker for transformation into AML.

Pharmacoeconomics of TFR was discussed in two lectures – "The long-term impact of TFR on economics" by Dr François-Xavier Mahon and "Budget impact analysis of discontinuing TKIs in patients with CML achieving a complete molecular response by using probabilistic Markov approach" by Dr Antoine Benard. Summary of the statistical finding was probability that TKI discontinuation is more expensive than TKI continuation in 200 patients/year is 3.5 and 11.8, if using branded and generic imatinib, respectively. Honestly, the lectures did not really excite me because it is pretty obvious TFR is much likely cost saving. Pertaining to generic imatinib, a poster caught my attention – "Comparison of the Efficacy of Chinese Generic Imatinib with Branded Imatinib As Frontline Therapy in Patients with Newly Diagnosed Chronic Myeloid Leukemia" by Xuelin Dou, Yazhen Qin, Yueyun Lai, Hongxia Shi, Xiaojun Huang, Qian Jiang, which showed similar efficacy between Chinese generic imatinib and branded imatinib in over 400 CML patients, who were enrolled since 2013. I talked to Dr Xuelin Dou and Dr Qian Jiang. I was told that there were two types of generic imatinib produced in China, which are approved by China government after they fulfilled the pharmacology-related requirement needed by law. These two generics was started to be produced after branded imatinib lost its patency in October 2013. Dr Qian Jiang started using one of the generics, presented in the poster, since then. Of course, I asked the most important question – the cost of the generic, after conversion, is about RM400 per month.

One question about TFR that I was looking for answer in this conference was probability of relapse after stopping TKI for more than 2 years. It was answered in two presentations. The first presentation presented the probability is ~11% after 3 years of stopping TKI. "Tyrosine kinase inhibitors discontinuation in CML patients: a meta-analysis of studies over the last 10 years" presented by Dr Stephanie Dulucq said probability of relapse beyond 24 months was not assessed but eight studies reported late molecular relapse of 1.7% between 25 and 52 months. Anyway, for our MSIT patients who have stopped TKI and still remain TFR for more than 3 years, we need to continue monitoring them, for which we are monitoring them every 3 monthly rightfully.

With this, I end my brief report on this conference. A big thank you to Malaysia Society of Haematology for sponsoring me to attend this conference.

Sincerely,

Prof Dr Kuan Jew Win