CHAPTER 5

DISCUSSION, RECOMMENDATIONS AND CONCLUSION

5.1 Introduction

In patients with B-ALL with *BCR-ABL1*, the evaluation of MRD is important in the management of B-ALL with *BCR-ABL1* to identify high-risk patients who would benefit from MRD-directed therapy. Haematologists use MRD-directed therapy to guide their decision making as to whether to intensify or deescalate leukaemia treatment in these patients. The evaluation of MRD can also identify patients who are more likely to benefit from stem cell transplantation (SCT) when patients enter complete remission for the first time (CR1). There are many methods for MRD detection, however, specific for B-ALL with *BCR-ABL1*, detection and quantification of the *BCR-ABL1* fusion gene transcript by quantitative PCR (qPCR) is the most important tool. A cut-off point of *BCR-ABL1* detected at 0.01% or 10^4 of nucleated cell from a bone marrow sample is used to stratify patients risk. *BCR-ABL1* transcripts detected below this limit are termed a complete molecular response (CMR). However, the impact of achieving CMR with B-ALL with *BCR-ABL1* remains undefined. Therefore, a time-point analysis of the quantification of the *BCR-ABL1* transcript could reveal the prognostic impact of achieving CMR in these patients towards the outcome of treatment.

5.2 Summary and Discussion of Findings

It has been widely accepted that MRD monitoring is paramount when considering the best course of treatment options for patients (Holowiecki et al., 2008; Lussana et al.,

2016). MRD monitoring requires high laboratory expertise and remains costly in developing countries. However, unlike chronic myeloid leukaemia, the germane response of MRD to chemotherapy on long-term outcome in ALL with *BCR-ABL1* has not been clearly defined. With our low nonrelapse mortality rate in matched sibling donor transplants, it was further justifiable to transplant ALL patients with standard risk in CR1, given significantly higher relapse and lower DFS if not transplanted. This echoed earlier observations of UKALL/RCOG 2993 studies which showed the survival difference between transplanted and nontransplanted cohort was significant even in standard-risk ALL patients (Goldstone et al., 2008), without MRD monitoring or identification of high-risk genetic markers. Reports showing successful transplants in CR2 with a curative potential of 25-30% have been reported (Gupta et al., 2013; Terwilliger & Abdul-Hay, 2017). However, these reports were highly selective and should not influence decisions against previous transplants. In our retrospective observation, other factors such as age, sex, and *BCR-ABL1* status did not affect OS and DFS. Our 2012-2018 transplanted cohort showed superior 3-year OS compared to the 2006-2011 cohort (Table 3). This was most likely due to the better selection of patients, improved supportive care, and the availability of TKI for ALL with *BCR-ABL1* in the previous cohort of patients.

We have shown that *BCR-ABL1* quantitation pre-transplant carried a significant prognostic outcome. These findings suggest that patients treated with chemotherapy and TKI who achieve MMR end-of-treatment at CR1 have excellent long-term survival. Optimal timing of MRD assessment may vary across TKI; however, end-of-treatment or pretransplant has proven to be extremely informative, factoring into the decision-

making and counselling process. On the contrary, MRD levels at earlier time points did not retain their statistical power in multivariate analyzes. Patients who achieved CMR at 3 months had better OS and DFS with chemotherapy or allogeneic SCT. Although there was a trend toward better survival among chemotherapy-treated patients, this was not statistically significant. The higher nonrelapsed mortality in patients who underwent allogeneic SCT may contribute to the discrepancy. However, the relapse rate was still higher in the chemotherapy group. Therefore, chemotherapy plus TKI may be a choice for patients who achieved early CMR but were unwilling to undergo SCT. Relapse or disease progression after transplantation remains a problem in allogeneic SCT (Socié et al., 1999). There is a need to address this outcome, as patients have an extremely poor prognosis. Novel immunotherapies such as Inotuzumab and Blinatumomab, as well as chimeric antigen receptor T cell therapy (CAR-T), have provided an opportunity for patients with relapsed and refractory ALL patients (Jabbour et al., 2018; Terwilliger & Abdul-Hay, 2017). Blinatumomab has been shown to eliminate positivity for MRD in ALL patients and has led to better survival outcomes post-transplant (Topp et al., 2011). There were a total of six patients with the *BCR-ABL1* level in TP3 <0.1% who either declined a transplant option or were not available. Only one patient remained alive at the time of the census, three patients were deceased, and two patients did not follow-up.

Our study focused on allogeneic SCT in the largest cohort of adult B-ALL with *BCR-ABL1* in Malaysia. Its retrospective nature makes it a true reflection of real-world practice in this part of the world. This is also one of the few studies that have a multiethnic group of patients. However, this study design also has inherent limitations

where variables related to disease characteristics and cytogenetic profiles were missing or unavailable. The MRD data was also incomplete in earlier patient data sets. Patients were also unable to be further classified on the basis of additional genetic mutations. A multicentre approach and collaboration are required to determine a more precise survival outcome.

5.3 Implications of The Study

This research was a retrospective observational descriptive study and was subject to the inherent limitations of retrospective analysis. During the course of the investigation, there was incomplete data collection as some patients did not comply with the follow-up date given. The transition from transcribed patient medical records to the integrated hospital information system without paper also made it challenging in some various ways to retrieve the required relevant clinical data that were not entered into the system during the transition. Furthermore, the time point for *BCR-ABL1* monitoring was different as it would depend on when treatment was started for each individual patient. Data not available on the hospital information system were obtained by tracking the hardcopy of patient notes at the medical records office or in the laboratory.

However, the current work is important because it shows real-world experience in assessing the patient's prognosis and informs clinicians of the expected outcome to better risk-stratify patients and preparing patients on what is expected of treatment and providing the best outcome for patients.

5.4 Recommendations of The Study

Future prospective trials are needed to evaluate the effectiveness of MRD monitoring for risk stratification of patients with B-ALL with *BCR-ABL1*. The impact of using different generations of TKI on patient outcomes also warrants further evaluation. The current work may be used as a surrogate for Asian countries and could potentially be used as a platform or reference point to design future prospective trials. Multicentre participation should also be taken into account.

5.5 Conclusion

In conclusion, MMR at the end of treatment was associated with a lower relapse rate and higher DFS among ALL with *BCR-ABL1* who underwent allogeneic SCT. This suggests that although frequent molecular monitoring and intervention are required for patients who do not show a reduction in *BCR-ABL1* transcript levels, only levels at the end of treatment were most useful in predicting the outcome after transplantation.

APPENDIX

Appendix 1: NMRR registration and MREC approval Ministry of Health Malaysia

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(*Medical Research & Ethics Committee*)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Kompleks Institut Kesihatan Negara
Blok A, No 1, Jalan Setia Murni U13/52,
Seksyen U13, Bandar Setia Alam,
40170 Shah Alam, Selangor.
Tel: 03-3362 8888/8205

Ref : KKM/NIHSEC/ P19-2212 (6)
Date: 11-October-2019

DR CHONG SIEW LIAN
HOSPITAL AMPANG

DR TAN SEN MUI
HOSPITAL AMPANG

Dear Sir/ Mdm,

ETHICS INITIAL APPROVAL: NMRR-19-2833-47785 (IIR)
IMPACT OF MOLECULAR RESPONSE ON SURVIVAL AMONG ALLOGENEIC STEM CELL TRANSPLANTATION RECIPIENTS WITH B-LYMPHOBLASTIC LEUKAEMIA WITH BCR-ABL1

This letter is made in reference to the above matter.

2. The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has provided ethical approval for this study. Please take note that all records and data are to be kept strictly **CONFIDENTIAL** and can only be used for the purpose of this study. All precautions are to be taken to maintain data confidentiality. Permission from the District Health Officer / Hospital Administrator / Hospital Director and all relevant heads of departments / units where the study will be carried out must be obtained prior to the study. You are required to follow and comply with their decision and all other relevant regulations, including the Access to Biological and Benefit Sharing Act 2017.

3. The investigators and study sites involved in this study are:

   CLINICAL RESEARCH CENTRE (CRC), AMPANG HOSPITAL
   Dr Chong Siew Lian (Penyelidik Utama)

   CLINICAL TRIAL UNIT, AMPANG HOSPITAL
   Dr Tan Sen Mui (Penyelidik Utama)

   HOSPITAL AMPANG
   Dr Jameela Sathar
   Dr Leong Tze Shin
   Dr Ong Tee Chuan
   Dr Roszymah Binti Hamzah
   Dr Tan Sen Mui (Penyelidik Utama)
   Hon Siong Leng
   Nur Liyana binti Mohd Ramli
   Law Kian Boon

4. The following study documents have been received and reviewed with reference to the above study:

KKM/NIHSEC/ P19-2212 (6)

Documents received and reviewed with reference to the above study:

1. Study Protocol_Version_1, dated 04-06-2019
2. Study Clinical Report Form (CRF) / Data Collection Form Version_ 1, dated 04-06-2019
3. Investigator's documents: Declaration of Conflict of Interest (COI), IA-HOD-IA, and CV:
   a) Dr Chong Siew Lian (Penyelidik Utama)
   b) Dr Jameela Sathar
   c) Dr Leong Tze Shin
   d) Dr Ong Tee Chuan
   e) Dr Roszymah Binti Hamzah
   f) Dr Tan Sen Mui (Penyelidik Utama)
   g) Hon Siong Leng
   h) Nur Liyana binti Mohd Ramli
   i) Law Kian Boon

5. Please note that ethical approval is valid until **10-October-2020**. The following are to be reported upon receiving ethical approval. Required forms can be obtained from the Medical Research Ethics Committee (MREC) website (**http://www.nih.gov.my/mrec**).
   i. **Continuing Review Form** has to be submitted to MREC within 2 month (60 days) prior to the expiry of ethical approval.
   ii. **Study Final Report** upon study completion to the MREC.
   iii. Ethical approval is required in the case of **amendments / changes** to the **study documents/ study sites/ study team**. MREC reserves the right to withdraw ethical approval if changes to study documents are not completely declared

6. This study involves the following methods:

   i. Retrospective
   ii. Medical record

7. Please take note that the reference number for this letter must be stated in all correspondence related to this study to facilitate the process.

Comments (if any): Nil

Project Sites:
CLINICAL RESEARCH CENTRE (CRC), AMPANG HOSPITAL
CLINICAL TRIAL UNIT, AMPANG HOSPITAL
HOSPITAL AMPANG

Decision by Medical Research & Ethics Committee:
(√) Approved
( ) Disapproved

Date of Approval : 11-October-2019

DR HJH SALINA ABDUL AZIZ
Chairperson
Medical Research & Ethics Committee
Ministry of Health Malaysia
MMC No: 27117

s.k. HRRC Hospital Ampang, Selangor

ZUZ/Approval2019/Mrecshare

Appendix 2: Article published in Blood Res 2021; 56(3): 175-183. Published online: 30 September 2021 DOI: https://doi.org/10.5045/br.2021.2021045

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ORIGINAL ARTICLE

Impact of timely *BCR-ABL1* monitoring before allogeneic stem cell transplantation among patients with *BCR-ABL1*-positive B-acute lymphoblastic leukemia

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Background
With the emergence of tyrosine kinase inhibitors and the incorporation of stringent measurable residual disease (MRD) monitoring, risk stratification for *BCR-ABL1*-positive acute lymphoblastic leukemia (ALL) patients has changed significantly. However, whether this monitoring can replace conventional risk factors in determining whether patients need allogeneic stem cell transplantation is still unclear. This study aimed to determine the impact of *BCR-ABL1* monitoring on the outcome of patients with *BCR-ABL1*-positive ALL after allogeneic stem cell transplantation.

Methods
We retrospectively analyzed the survival outcome of patients with *BCR-ABL1*-positive ALL based on the quantification of *BCR-ABL1* at 3 timepoints: the end of induction (timepoint 1), post-consolidation week 16 (timepoint 2), and the end of treatment for patients who were either transplant-eligible or non-transplant eligible (timepoint 3).

Results
From 2006 to 2018, a total of 96 patients newly diagnosed with *BCR-ABL1*-positive ALL were treated with chemotherapy and tyrosine kinase inhibitors. Thirty-eight (41.3%) patients achieved complete remission, and 33 patients underwent allogeneic stem cell transplantation. Our data showed that pre-transplant MRD monitoring by real-time quantitative polymerase chain reaction had the highest correlation with survival in patients with *BCR-ABL1*-positive ALL, especially for those who underwent allogeneic stem cell transplantation.

Conclusion
Patients without MRD pre-transplantation had superior survival compared with those who had MRD, and they had excellent long-term outcomes after allogeneic stem cell transplantation.

Key Words ALL, BCR-ABL1, Philadelphia, Survival, TKI

INTRODUCTION

B-cell acute lymphoblastic leukemia (B-ALL) is a hematological malignancy in which the bone marrow produces neoplastic lymphoblasts that are committed to the B-cell lineage. The complexity and spectrum of hematological malignancies highlight the importance of clinicopathologic correlation with the availability of ancillary studies [1]. Approximately 20–30% of adult ALLs harbor the Philadelphia chromosome, which produces the *BCR-ABL1* fusion gene that has a significant prognostic and survival impact in patients [2]. About half of these cases harbor a translocation that produces the p210 fusion protein, which is the characteristic transcript