

IMPACT OF *BCR-ABL1* MONITORING AMONG PATIENTS WITH *BCR-ABL1*-POSITIVE B-ACUTE LYMPHOBLASTIC LEUKEMIA

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AUTHOR DECLARATION

I declare that this dissertation is entirely my own original work.

I declare that, except where fully referenced direct quotations have been included, no aspect of this dissertation has been copied from any other source.

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ABSTRAK

Leukemia limfoblastik akut atau *Acute lymphoblastic leukaemia (ALL)* dengan *BCR-ABL1* membawa kepada risiko yang tinggi untuk relaps serta prognosis yang teruk. Akses kepada perencat tyrosine kinase sebagai salah satu strategi rawatan telah mengubah stratifikasi risiko untuk pesakit ALL yang mempunyai gen tertaup ini. Memandangkan *BCR-ABL1* dikuantifikasi secara rutin untuk pemantauan penyakit mieloproliferatif, penggabungan kuantifikasinya melalui reaksi rantai polimerase pada masa nyata boleh dijadikan sebagai parameter yang boleh dipercayai sebagai pemantau sisa penyakit atau *measurable residual disease (MRD)* untuk ALL yang mempunyai *BCR-ABL1*. Sama ada ini telah menggantikan faktor risiko konvensional dalam menentukan pesakit mana yang memerlukan transplan atau tidak masih belum ditentukan. Kajian ini adalah bertujuan untuk menentukan kesan pemantauan *BCR-ABL1* pada pesakit ALL dengan *BCR-ABL1* terhadap keputusan mereka selepas pemindahan sel stem alogenik. Kami menganalisa hasil kelangsungan hidup pesakit ini secara retrospektif berdasarkan kuantifikasi *BCR-ABL1* pada tiga titik-masa; titik-masa pertama pada akhir induksi, titik-masa kedua pada minggu ke-16 selepas konsolidasi, dan titik-masa ketiga pada akhir rawatan pesakit yang sama ada layak untuk transplan atau tidak layak untuk transplan. Dari tahun 2006 hingga 2018, sejumlah 96 pesakit dewasa yang baru didiagnosis dengan Leukemia Limfoblastik Akut dengan *BCR-ABL1* telah dirawat dengan kemoterapi dan perencat tyrosine kinase. Tiga puluh lapan (41.3%) mencapai remisi keseluruhan dan 33 pesakit telah menjalani pemindahan sel stem alogenik. Data kami menunjukkan bahawa pemantauan sisa penyakit melalui tindak balas rantai polimerase kuantitatif pada masa nyata yang dilakukan sebelum transplan

menunjukkan hubung kait kelangsungan hidup yang tertinggi dalam pesakit ALL dengan *BCR-ABL1* terutamanya bagi mereka yang menjalani transplan sel stem alogenik. Pesakit yang mempunyai MRD negatif pra-transplan, mempunyai kelangsungan hidup yang lebih tinggi berbanding mereka yang MRD positif dan menunjukkan hasil jangka panjang yang cemerlang selepas transplan sel stem alogenik. Dengan kemunculan perencat/inhibitor tyrosine kinase dan penggabungan pemantauan penyakit sisa yang boleh diukur dengan ketat, stratifikasi risiko untuk ALL dengan *BCR-ABL1* telah berubah dengan ketara.

ABSTRACT

Acute lymphoblastic leukaemia (ALL) with *BCR-ABL1* confers a high risk of relapse and a poor prognosis. Access to the tyrosine kinase inhibitor as part of the treatment strategy has changed the risk stratification for ALL patients harbouring this fusion gene. As *BCR-ABL1* is routinely quantified for the monitoring of its myeloproliferative counterpart, incorporation of its quantification by real-time polymerase chain reaction could be a reliable parameter for the monitoring of measurable residual disease (MRD) for ALL with *BCR-ABL1*. Whether this has replaced conventional risk factors in deciding whether patients would need a transplant or not is yet to be determined. This study aimed to determine the impact of *BCR-ABL1* monitoring in patients with ALL with *BCR-ABL1* on their outcome after allogeneic stem cell transplantation. We retrospectively analysed the survival outcome of these patients based on the quantification of *BCR-ABL1* at three time-points; time-point 1 at the end of induction, time point 2 at post-consolidation week 16, and time point 3 at the end of treatment for patients who were transplant-eligible or nontransplant eligible. From 2006 to 2018, a total of 96 adult patients newly diagnosed with acute lymphoblastic leukemia with *BCR-ABL1* were treated with chemotherapy and a tyrosine kinase inhibitor. Thirty-eight (41.3%) achieved overall remission; 33 patients underwent an allogeneic stem cell transplant. Our data showed that residual disease monitoring by real-time quantitative polymerase chain reaction performed prior to transplantation showed the highest survival correlation in ALL with patients with *BCR-ABL1*, especially for those who underwent allogeneic stem cell transplantation. Patients with MRD negative before transplantation had better survival compared to those who were MRD positive and showed excellent long-term outcomes after allogeneic stem cell transplantation.

With the emergence of tyrosine kinase inhibitors and the incorporation of stringent, measurable residual disease monitoring, risk stratification for ALL with *BCR-ABL1* has changed significantly.



مُلَخَّص

خطورة عالية للنكس وإنذار سيئ. أدى $BCR-ABL1$ مع جين ALL يحمل ابيضاض الدم الليمفاوي الحاد (الوصول إلى مثبطات التيروزين كيناز كجزء من استراتيجية العلاج إلى تغيير تصنيف الخطورة لجميع المرضى الذين لديهم هذا الجين المندمج.

بشكل روتيني لأجل مراقبة ما يقابله من تكاثر نقوي، فإن اعتماد قيمته $BCR-ABL1$ بما أنه يتم قياس كمية المحددة كميًا بواسطة تفاعل البوليميراز المتسلسل في الوقت الفعلي يمكن أن يكون معياراً موثقاً لرصد الحد $BCR-ABL1$ مع جين ALL) لابيضااض الدّم الليمفاوي الحاد (MRD الأدنى من المرض المتبقي (لم يتم بعد تحديد ما إذا كان استخدام هذه القيمة قد ينوب عن استخدام عوامل الخطر التقليدية في تحديد المرضى في المرضى $BCR-ABL1$ الذين يحتاجون إلى عملية زرع أم لا. هدفت هذه الدراسة إلى تحديد تأثير مراقبة على نتائجهم بعد زرع الخلايا الجذعية المثلية. $BCR-ABL1$ ولديهم جين ALL الذين يعانون من

في ثلاث نقاط زمنية؛ $BCR-ABL1$ قمنا بتحليل نتائج بقيا هؤلاء المرضى رجعيًا اعتماداً على القياس الكمي لـ النقطة الزمنية 1 في نهاية التحفيز، النقطة الزمنية 2 في الأسبوع 16 ما بعد الاندماج، والنقطة الزمنية 3 في نهاية العلاج للمرضى سواء كانوا مؤهلين للزراعة أو غير مؤهلين للزراعة.

$BCR-$ تم بين عامي 2006 و 2018 علاج 96 مريض بالغ مُشخّص حديثاً بسرطان الدم اللمفاوي الحاد مع العلاج الكيميائي والعلاج بمثبطات التيروزين كيناز. حقق ثمانية وثلاثون (41.3%) منهم تعافياً $ABL1$ إجمالياً؛ خضع 33 مريض منهم لعملية زرع الخلايا الجذعية المثلية. أظهرت بياناتنا أن مراقبة الحد الأدنى المتبقي من المرض عن طريق تفاعل البوليميراز المتسلسل الكمي في الوقت الفعلي الذي تم إجراؤه قبل الزرع خاصّةً أولئك الذين خضعوا لعملية $BCR-ABL1$ الذين لديهم جين ALL يملك أعلى ارتباط مع البقاء لدى مرضى زرع الخلايا الجذعية المثلية.

إيجابية، MRD سلبية قبل الزرع بنسبة بقيا أعلى مقارنة مع أولئك الذين كانت MRD يتمتع المرضى الذين لديهم ALL ولقد أظهروا نتائج ممتازة على المدى الطويل بعد زرع الخلايا الجذعية المثلية. لقد تغير تصنيف خطورة

بشكل كبير مع ظهور مثبطات التيروزين كيناز وإجراء مراقبة صارمة للحدّ *BCR-ABL1* المترافق مع جين
الأدنى المتبقّي من المرض.

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TABLES OF CONTENTS

AUTHOR DECLARATION	i
ACKNOWLEDGEMENTS.....	ii
ABSTRAK	iii
ABSTRACT	v
ملخص	vii
TABLES OF CONTENTS	ix
LIST OF TABLES.....	xii
LIST OF FIGURES.....	xiii
LIST OF APPENDICES	xiv
LIST OF ABBREVIATIONS.....	xv
CHAPTER 1	17
INTRODUCTION	17
1.1 Introduction.....	17
1.2 Background of the Study	18
1.3 Problem Statement.....	21
1.4 Research Questions	22
1.5 Objectives of the Study	22
1.5.1 General Objective	22
1.5.2 Specific Objectives	22
1.6 Significance of The Study.....	23
1.7 Scope of the Study	24
1.8 Research Conceptual Framework	24
1.9 Operational Definitions.....	26
1.9.1 BCR-ABL1 Molecular Monitoring	26
1.9.2 Complete Haematological Response (CHR)	26
1.9.3 Complete Molecular Response (CMR).....	27
1.9.4 Major Molecular Response (MMR).....	27
1.9.5 First Complete Remission (CR1).....	27
1.9.6 Engraftment	27
1.9.7 Disease Relapse	28
1.9.8 Disease-free Survival (DFS).....	28
1.9.9 Overall Survival (OS)	28
CHAPTER 2	29
LITERATURE REVIEW.....	29

2.1 Overview of Acute Lymphoblastic Leukaemia	29
2.2 <i>BCR-ABL1</i> in B-Acute Lymphoblastic Leukaemia	31
2.3 Minimal Residual Disease Monitoring in B-ALL with <i>BCR-ABL1</i>	35
2.4 Management of B-ALL with <i>BCR-ABL1</i>	36
2.5 Gap Analysis	41
CHAPTER 3	43
METHODOLOGY	43
2.1 Introduction	43
2.2 Research Design	43
2.3 Molecular Monitoring Strategy	44
2.4 Study Location	45
2.5 Population and Sampling	45
2.5.1 Inclusion Criteria	45
2.5.2 Exclusion Criteria	45
2.6 Research Instruments	45
2.6.1 Hospital Information System (HIS)	45
2.6.2 Laboratory Results	46
2.6.3 Data Collection	47
2.7 Statistical Analysis	47
CHAPTER 4	49
FINDINGS	49
4.1 Characteristics of Patients with ALL with <i>BCR-ABL1</i> in Hospital Ampang	49
4.2 Treatment Modalities and <i>BCR-ABL1</i> Monitoring	49
4.3 Outcomes of <i>BCR-ABL1</i> Positive B-ALL Patients	51
4.4 Characteristics of Transplanted Patients with B-ALL with <i>BCR-ABL1</i>	53
4.5 Transplant Modalities and Outcome of Allogeneic Stem Cell Transplant	55
4.7 Patients Achieving CMR Using <i>BCR-ABL1</i> Transcript Levels at Different Time Points	59
CHAPTER 5	67
DISCUSSION, RECOMMENDATIONS AND CONCLUSION	67
5.1 Introduction	67
5.2 Summary and Discussion of Findings	67
5.3 Implications of The Study	70
5.4 Recommendations of The Study	71
5.5 Conclusion	71
APPENDIX	72

REFERENCES	75
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LIST OF TABLES

Table 1: Chemotherapy regimen for B-ALL with <i>BCR-ABL1</i> at Hospital Ampang ..	37
Table 2: Long-term results of TKI-based clinical trials for adult Ph+ (patients in complete hematologic remission), with an emphasis on allogeneic stem cell transplantation.	38
Table 3: Baseline patient characteristics.....	50
Table 4: Treatment modalities and molecular monitoring of <i>BCR-ABL1</i>	51
Table 5: Characteristics of Characteristics of transplanted patients.....	54
Table 6: Transplant modalities and outcomes in patients with B-ALL with <i>BCR-ABL1</i>	56
Table 7: Univariable analysis of factors predictive of OS.....	61
Table 8: Multivariable analysis of factors predictive of OS and DFS in transplant patients.	62

LIST OF FIGURES

Figure 1: Number of stem cell transplants performed from 1999 to 2019.	25
Figure 2: Conceptual framework of the research	26
Figure 3: Schematic representation of the structure of the breakpoint cluster region (BCR) proto-oncogene tyrosine protein kinase (<i>ABL1</i>) gene and protein.....	33
Figure 4: Transplantation outcome, OS according to <i>BCR-ABL1</i> at certain time points. (A) Post-induction MRD (B) Post-consolidation week 16 (C) End of treatment (D) The overall cohort	64
Figure 5: Transplantation outcome, DFS according to <i>BCR-ABL1</i> at certain time points. (A) Post-induction MRD (B) Post-consolidation week 16 (C) End of treatment (D) The overall cohort	66

LIST OF APPENDICES

Appendix 1: NMRR registration and MREC approval Ministry of Health of Malaysia	72
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	74



LIST OF ABBREVIATIONS

aGVHD	Acute graft-versus-host disease
AML	Acute myeloid leukaemia
AYA	Adolescent and young adult
B-ALL	B-Acute Lymphoblastic Leukaemia
<i>BCR-ABL1</i>	Breakpoint Cluster Region-Abelson 1 fusion protein
BFM	Berlin-Frankfurt-Munich protocol
cGVHD	Chronic GVHD
CLAEG	Cladribine, VP16, AraC, GCSF, methotrexate and dexamethasone regime
CML	Chronic myeloid leukaemia
CML-N	Neutrophilic-chronic myeloid leukaemia
CMR	Complete molecular response
CMV	Cytomegalovirus
CNS	Central nervous system
CR1	First complete remission
DFS	Disease-free survival
FISH	Fluorescence in-situ hybridization
FLAG-IDA	Fludarabine, AraC, Idarubicin, GCSF, methotrexate, dexamethasone regime
GMALL 07/2003	vincristine, daunorubicin, dexamethasone, L-asparaginase, methotrexate, rituximab, GCSF regime
GVHD	Graft-versus-host disease.
HSCT	Haemopoietic stem cell transplant
Hyper-CVAD	VP16, GCSF, rituximab dexamethasone, vindesine, methotrexate, folinic acid, AraC, regime
IS	International system of units
LC	Light cycle
MMR	Major molecular response
MRD	Measurable residual disease

MSD	Matched sibling donor
MUD	Matched unrelated donor
OS	Overall survival
RCPA	Royal College of Pathologists of Australasia
RIC	Reduced intensity conditioning
SCT	Stem cell transplant
TBI	Total body irradiation
TCR	T-cell receptor
TKI	tyrosine kinase inhibitor
TP	Time-point
TP1	Time-point 1, post-induction
TP2	Time-point 2, post-consolidation or week 16
TP3	Time-point 3, end-of-treatment
Ph	Philadelphia chromosome
qRT-PCR	Quantitative real-time polymerase chain reaction
UKALL	International ALL Trial
UKNEQAS	United Kingdom National External Quality Assessment Service
VDJ	Variability Diversity Joining
WCC	White cell count
WHO	World Health Organization