UNIVERSITI PUTRA MALAYSIA

EXPRESSION OF SURVIVAL AND APOPTOTIC MOLECULES IN RESPONSE TO EARLY STAGE CHEMOTHERAPY IN ACUTE MYELOID LEUKAEMIA

STEPHNIE YIAU KANG XIAN

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By

STEPHNIE YIAU KANG XIAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

December 2013

DEDICATION

To my beloved family and cherished friends,

Your support and encouragements were the pillars of my strength to finish this journey

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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December 2013

Chairman : Maha Abdullah, PhD
Faculty : Medicine and Health Sciences

Acute myeloid leukaemia (AML) is a haematological malignancy characterised by a predominance of myeloid precursor cells that leads to death if not treated. A major factor in the failure of AML chemotherapy is due to the acquisition of multidrug resistance (MDR) by the malignant myeloblast. Factors such as cytokines, activation of signalling pathway mediators and Bcl-2 family proteins contributes to cell survival, thus leading to MDR. Bone marrow aspirate was collected a month after induction therapy to determine complete remission (CR). It is postulated that the treatment outcome could be determined during early induction therapy through the expression pattern of cellular molecules in peripheral blood. The expression patterns of stem cell marker, CD34, c-Kit receptor (CD117), cytokines and their receptors, signalling mediators of the PI3K/Akt and MAP kinase pathway, and Bcl-2 family proteins were observed in the peripheral blood of AML patients collected before and/or during Day 3 of induction therapy with anthracycline and cytarabine arabinoside (Ara-C). Expression were measured using flow cytometry for the percentage of cells expressing and geometric mean fluorescent intensity (MFI), as well asRT-PCR. Results showed that the percentage of cells expressing IL-1β ($p=0.028$), the MFI of IL-18Rα ($p=0.01$), MFI ($p=0.007$) and mRNA levels ($p=0.038$) of TNF-α, MFI of DR5 ($p=0.02$) and MFI of pAkt-T308 ($p=0.038$) was found to be significantly higher in samples of sensitive patients prior to induction therapy. Untreated resistant samples were found to have significantly higher MFI for pFKHR ($p=0.05$). During induction therapy, we found that in sensitive samples,IL-18Rα was found to be significantly higher in the percentage of expressing cells ($p=0.014$) and the MFI ($p=0.02$)was higher as well. These treated sensitive samples were also found to have significantly higher pp38 MFI ($p=0.039$). Treated resistant samples were found to have significantly higher percentage of CD34 ($p=0.028$) and pBAD ($p=0.014$) expressing cells. Spearman Rank-order correlation analysis showed that there is no correlation between the MFI and the mRNA transcript of cytokine and its receptors. Similar correlations analysis

were also observed between cytokines and receptors with signalling mediators and apoptotic molecules, pBAD and Bim. Some of these correlations corresponded to the cytokines role in apoptosis and survival but there are some contradictions. Molecules such as DR5, CD34, pFKHR and pBAD are potential prognostic markers of treatment outcome but some might not be suitable markers of treatment outcome at the early stages of induction therapy.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

EXPRESI MOLEKUL KEMANDIRAN DAN APOPTOTIK SEBAGAI TINDAK BALAS TERHADAP KEMOTERAPI PERINGKAT AWAL LEUKEMIA MIELOID AKUT

Oleh

STEPHNIE YIAU KANG XIAN

Disember 2013

Pengerusi : Maha Abdullah, PhD
Fakulti : Perubatan dan Sains Kesihatan

Leukemia mieloid akut (AML) adalah kanser hematologi yang dicirikan oleh penguasaan sel-sel pelopor mieloid yang membawa maut jika tidak dirawat. Sebab utama dalam kegagalan kemoterapi AML adalah kekebalan sel myeloblast malignan terhadap beraneka jenis ubat, suatu fenomena yang dikenal sebagai MDR. Faktor-faktor seperti sitokina, pengaktifan pengantara laluan transduksi isyarat dan kumpulan protein Bcl-2 menyumbang kepada kemandirian sel dan seterusnya MDR. Sampel kandungan sumsum tulang diambil sebulan selepas terapi induksi untuk menentukan status sembuh sempurna (CR). Diandaikan bahawa keputusan akhir hasil daripada rawatan dapat ditentukan semasa terapi induksi awal melalui tindak balas biologi antara molekul-molekul sel dalam darah. Corak ekspresi penanda sel induk, CD34, reseptor c-Kit (CD117), sitokina dan reseptor-reseptornya, pengantara isyarat laluan PI3K/Akt dan MAP kinase, dan kumpulan protein Bcl-2 dikaji daripada darah pesakit AML yang dikumpul sebelum dan/atau semasa hari ketiga terapi induksi dijalankan dengan antrasiklin dan sitosina arabinosida (Ara-C) dengan menggunakan kaedah sitometri aliran dan RT-PCR. Keputusan mendedahkan bahawa sebelum terapi induksi, peratusan sel yang menunjukkan IL-1β, MFI IL-18Rα, MFI dan mRNA TNF-α, DR5 dan MFI pAkt-T308 adalah lebih tinggi dalam sampel sensitif. Didapati sampel rintang sebelum rawatan menunjukkan MFI pFKHR yang jauh lebih tinggi. Semasa terapi induksi, sampel sensitif yang mempunyai IL-18Rα memaparkan peratusan bilangan sel dan MFI yang lebih tinggi. Sampel sensitif yang dirawati ini juga menunjukkan pp38 MFI yang lebih tinggi. Sampel rintang yang dirawati didapati mempunyai jauh lebih tinggi peratusan sel-sel yang expresi CD34 dan pBAD. Penelitian menunjukkan bahawa hubungan antara sitokina dan reseptor tidak berkaitan dengan transkrip mRNA sitokina. Hubungan antara sitokina dan reseptor dengan pengantara isyarat dan molekul apoptotik, pBAD dan Bim, juga ditinjau. Sesetengah analisis hubungan tersebut sepadan dengan peranan sitokina dalam apoptosis dan kemandirian tetapi terdapat beberapa keputusan yang bercanggahan. Didapati bahawa

tahap rendah DR5 dan tahap tinggi pFKHR sebelum terapi induksi berpotensi menunjukkan rintangan-kimo manakala tahap tinggi CD34 dan pBAD semasa induksi menunjukkan rintangan-kimo. Oleh itu, molekul seperti DR5, CD34, pFKHR dan pBAD adalah potensi ramalan penanda untuk hasil rawatan manakala sesetengah mungkin tidak sesuai penanda hasil rawatan pada awal terapi induksi.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science**.** The members of the Supervisory Committee were as follows:

Maha Abdullah, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Eusni Rahayu Mohd Tohit, MBBS (Malaya), MPath (UKM, Mal)
Senior Medical Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Dato' Dr. Chang Kian Meng, MBBS (Malaya), MRCP (UK), FRCP (London), FRCPA (Haem)
Consultant Hematologist and Head of Department
Hospital Ampang
(Member)

BUJANG BIN KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 03 April 2014

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) were adhered to.

Signature: _____
Name of Chairman of Supervisory Committee: Professor Dr. Maha Abdullah

Signature: _____
Name of Member of Supervisory Committee: Dr. Eusni Rahayu Mohd Tohit

Signature: _____
Name of Member of Supervisory Committee: Dato' Dr. Chang Kian Meng,

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LIST OF ABBREVIATIONS

AML	acute myeloid leukaemia
Ara-C	cytarabine arabinoside
Ara-CTP	cytarabine arabinoside triphosphate
Ara-CMP	cytarabine arabinoside monophosphate
APML	acute promyeloid leukaemia
B2M	beta-2-microglobulin
BAD	Bcl-2-associated death promoter
BCP	2-Bromo-Phenol-Chloroform
BD	Becton and Dickinson
BMA	bone marrow aspirate
CALGB	Cancer and Leukaemia Group B
CO_2	carbon dioxide
CR	complete remission
dCyc	deoxycytidine kinase
DFS	disease-free survival
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
dNTP	deoxyribonucleotide triphosphates
DNR	Daunorubicin
EDTA	Ethylenediaminetetraacetic acid
FAB	French-American-British
FBS	foetal bovine serum
FITC	Fluorescein isothiocyanate
FKHR	forkhead in rhabdomyosarcoma
HIDAC	high dose intermittent Ara-C

IDA	Idarubicin
IL	interleukin
JNK	c-Jun N-terminal kinase
MIDAC	Mitoxontrone and arabinoside cytarabine
MAP	mitogen activated kinase
MFI	mean fluorescence intensity
min(s)	minute(s)
MKK	MAP kinase kinase
MKKK	MAP kinase kinase kinase
MMLV	murine leukaemia virus
PBS	Phosphate Buffered Saline
PI3K	Phosphoinositide 3-kinase
PE	Phycoerythrin
PerCP	Peridinin Chlorophyll
RNA	ribonucleic acid
RT	room temperature
S	serine
T	threonine
TAE	tris-acetate EDTA
TNF	tumour necrosis factor
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

Acute myeloid leukaemia (AML) is an infrequent but extremely malignant neoplasm which is responsible for a large number of cancer-related deaths. AML is a heterogeneous group of malignant haemapoietic precursor of the myeloid lineage. AML can be characterised by the predominance of immature cells as well as the loss of regular haemapoietic functions. If the disease is left untreated, the patient progresses towards death within weeks to months of clinical presentation (Johnstone et al., 2002).

In the United States of America, the age-adjusted incident of AML was reported to be 3.4 case/100,000 persons (Kanno et al., 2004b).According to the 2007 National Cancer Registry 3.1 percent of new cancer cases were reported to be myeloid leukaemia (Ariffin and Saleha, 2011). Childhood AML is rare (Karin et al., 1997) but the incidence increases at adulthood with a higher risk of occurance among the elderly (Johansson and Harrison, 2009).

Diagnosing AML successfully has always been a challenge for pathologists as the treatment hinges on the diagnosis. Various classifications for AML has been set, from the traditional FAB classification that depends on morphological and immunophenotypic evaluations, to the more recent WHO classification that utilises morphology, immunophenotyping and genetic abnormalities (Bennett et al., 1976; Vardiman et al., 2002).

Chemotherapy remains the standard therapeutic approach to treat the malignancy but little of the treatment regimen has changed over the past three decades ((Kimby et al., 2001). The chemotherapeutic drugs exert its cytotoxic effects on the cells by damaging DNA, lipid membrane and cellular bodies (Keesler et al., 1998). The targeted myeloblast is then killed by inducing apoptosis through a cascade of biochemical events (Kim et al., 2010).

Around 80% of patients who underwent the standard induction regimen achieved complete remission (CR)and is adequate for the younger patients (Stone et al., 2004). However, it is observed that elderly patients (>60 years) are highly resistant to the chemotherapeutic treatment and have poor overall outcomes (Leith et al., 1997b). However, the overall survival of AML from 2003 to 2009 was reported to be 22 to 25.7% with men having lower overall survival percentage (Howlander, 2012).

The current method of detecting drug resistance in AML is through the painful and invasive procedure of obtaining the patient's bone marrow aspiration. It is usually done approximately 3-4 weeks from the first day of induction therapy to observe the presence of malignant myeloblast in the marrow. Clinicians also tries to predict drug

resistance through several other prognostic markers such as age, white blood count and cytogenetic markers before chemotherapy treatment.

Multidrug resistance (MDR) remains a major hurdle to overcome in achieving CR in AML patients especially among the elderly patients. This is because the myeloblast are able to escape the drug induced apoptosis through overexpression of anti-apoptotic molecules. Previous studies has implicated immature phenotypic markers (Kim et al., 2006), a consecutive activation and up-regulation of mediator of survival pathway e.g. PI3K/Akt(Tazzari et al., 2008) and MAP kinase (Abedini et al., 2009) as well as increased expression of anti-apoptotic Bcl-2 family (Cory et al., 2003)protein as factors of drug resistance.

Previous study has shown that chemotherapy induces a change in the proteomic expression profile due to the induction of molecules and mediators of survival and apoptotic pathways (Devemy et al., 2001; Maha et al., 2009). Maha (2009) has observed that induction therapy is capable of inducing changes in expression of key signalling molecules of PI3K/Akt and MAP kinase pathway. Similarly, it was also observed that the cytokine expression changes when the patient undergoes induction therapy (Devemy et al., 2001; Maha et al., 2009). These changes in intracellular molecule expression are discovered to have an association with the patient's treatment outcome.

It is believed that the changes of these intracellular molecules caused by induction therapy are detectable in AML cells found in the peripheral blood and respond early in treatment. Therefore, they have the potential of being markers to monitor tumour cell response and predicting treatment outcome at the early stages of induction therapy.

This research attempts to study the peripheral blood of expression of surface phenotypic markers, various signalling mediators from survival pathways, cytokines and receptors; and Bcl-2 family protein in association with drug resistance at early induction of AML patients.

The objectives of this research are as follows:

- To determine the expression levels of surface markers, cytokines, signalling mediators and apoptotic related molecules in the peripheral blood of acute leukaemia samples before and during chemotherapy using flow cytometry;
- To determine the level of cytokine mRNA expression and correlate with cytokine protein expression in leukaemia samples before and during chemotherapy; and
- To correlate the expressionlevels of these molecules with treatment outcome.

In this study, it is hypothesised that:

1. Cytokines, IL-1β, IL-18, and IL-18 receptor are significantly increased in resistant AML samples during chemotherapy.
2. Cytokines, IL-6 and TNF-αare significantly decreased in resistant AML samples during chemotherapy.
3. Pro-survival mediators of signalling pathway including Akt, p38 and JNK are significantly increased in resistant AML samples during chemotherapy..
4. Pro-apoptotic mediators of signalling pathways including BAD, Bim, and FKHR are significantly decreased in resistant AML samples during chemotherapy.
5. Surface markers including CD34 and CD117 are significantly increased in resistant AML samples during chemotherapy.

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