CXCR4 Expression In Acute Myeloid Leukemia

Essay

Submitted in Partial fulfillment for master degree ***in Internal Medicine***

By:

Nour El Huda Hussein Abdulla
M.B., B.Ch.

Under Supervision of

Professor Dr. Hoda Ahmed Gad -Allah
Professor of Internal Medicine And Clinical Hematology
Faculty of medicine Ain Shams University

Dr. Nevine Nabil Mostafa
Lecturer of Internal Medicine and Hematology
Faculty of Medicine Ain Shams University

Dr. Gihan Mohamed Kamal shams El- Din
Lecturer of Internal Medicine and Hematology
Faculty of medicine Ain Shams University

Faculty of Medicine
Ain Shams University
2010

تأثير المستقبل الكيميائى الرابع فى اللوكيميا الميلودية الحادة

رسالـة

توطئه للحصول على درجة الماجستير فى الباطنة العامة

مقدمه من

الطبيبة/نورالهدى حسين عبدالله أحمد

بكالوريوس الطب والجراحة

تحت إشراف

الأستاذة الدكتورة / هدى أحمد جاد الله

أستاذ الباطنة العامة وأمراض الدم

كلية الطب . جامعة عين شمس

الدكتورة/ نيفين نبيل مصطفى

مدرس الباطنة العامة وأمراض الدم

كلية الطب . جامعة عين شمس

الدكتورة/ جيهان محمد كمال شمس الدين

مدرس الباطنة العامة وأمراض الدم

كلية الطب . جامعة عين شمس

كلية الطب

جامعة عين شمس

2010

List of content

List of Figures

List of Table

List of Abbreviations

APTT	Activated partial thromboplastin time
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
APL	Acute promyelocytic leukaemia
ATRA	All trans retinoic acid
BUN	Blood urea nitrogen
BMT	Bone marrow transplantation
CSF	Cerebrospinal fluid
CXCR4	Chemocine receptor 4
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CD	Cluster of differentiation
CAMAL	Common antigen of myelogenous leukaemia
CBC	Complete blood picture
CR	Complete remission
CT SCANS	Computarised tomography
Ara c	Cytarabine
DNA	Dinucelic acid
DIC	Disseminated intravascular coagulopathy
DLT	Dose limiting toxicities
DNR	Daunorubicin
FLT 3	Fetal liver tyrosine kinase 3
FISH	Fluorescent in situ hybridization
FAB	French American british system
Go	Gemtuzumab ozogamycin
GVHD	Graft versus host disease
G CSF	Granulocyte colony stimulating factor
HSCS	Hemopoietic stem cells
HLA	Human leukocyte antigen
HIF-1	Hypoxia inducible factor 1
INF G	Interferon gamma
ITD	Internal tandem duplications
KSP	Kinesin spindle protein

List of Abbreviations (Cont.)

LDH	Lactate dehydrogenase
MRI	Magnetic resonance imaging
MUD	Matched unrelated donor
MTD	maximal tolerated dose
MRD	Minimal residual disease
MHC	Minor histocomptability antigens
MLL	Mixed lineage leukaemia gene
mab	Monoclonal antibodies
M.M.	Multiple myeloma
MPD	Myeloproliferative syndrome
MDS	Mylodysplastic syndrome
NLCs	Neurse like cells
NHL	Non Hodgkin lymphoma
NOD/SCID	Non obese diabetes severe combined immunodeficiency mice
ORR	Over all response rate
OS	Over all survival
PSCT	Peripheral Stem cell transplantaion
PCR	Polymerase chain reaction
PT	Prothrombin time
SCLC	Small cell lung carcinoma
SCT	Stem cell transplantaion
SDF-1	Stromal cell derived factor -1
TDT	Terminal deoxynucleotidyl transferase
VLA -4	Very late antigen 4 integrins
VLA -5	Very late antigen 5 integrins
WBC	White blood cell count
WHO	World health organisation system

Acknowledgment

Firstly, I thank "God" for granting me the power to accomplish this work.

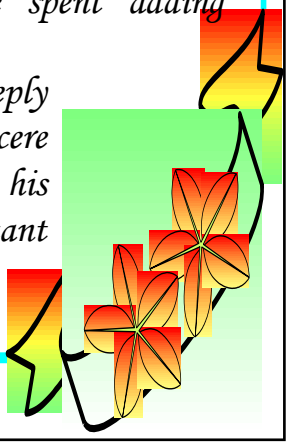
I find no words by which I can express my extreme thankfulness, deep appreciation and profound gratitude to my eminent **Professor Dr. Hoda Ahmed Gad-Allah,** *Professor of Internal Medicine, Faculty of Medicine, Ain Shams University, for giving me the privilege of working under her meticulous supervision and for her generous help, guidance, kind encouragement and great fruitful advice during supervision of this work.*

Grateful acknowledgment and deep appreciation are conveyed to **Dr. Nevine Nabil Mostafa** *Lecturer of Internal Medicine, Faculty of Medicine, Ain Shams University, for the great kindness, constant assistance and guidance.*

I am greatly honored to express my sincere appreciation and gratitude to **Dr. Gihan Mohamed Kamal** *Lecturer of Internal Medicine, Faculty of Medicine, Ain Shams University, for her kind supervision, enthusiastic guidance, constant support, illuminating discussion and valuable time she spent adding valuable suggestions and remarks.*

I am greatly thankful, grateful ,and deeply appreciating for my kind parents and my sincere husband **Mr. Ahmed Fathala Abdelmenam** *for his great help, minute to minute care and constant support.*

Nour El Huda Hussein Abdulla



الملخص العربي

تتصف اللوكيميا الحاده الميلود يه بالتكاثر الغير منتظم لخلايا الدم الاوليه، وخطورة هذا المرض تزداد مع تكاثر هذه الخلايا الاوليه فى النخاع العظمى ،حيث أن هذه الخلايا الاوليه تستطيع ان تخترق الدم ثم تتمركز فى أماكن اخرى خارج النخاع العظمى ،والتفاعل ما بين المواد الناتجه من هذه الخلايا و مستقبلات هذه المواد هو المسئول عن خروج هذه الخلايا الاوليه من النخاع العظمى إلى خارجه.

وعلى الرغم من التطورات فى فهم و علاج أنواع متعدده من الوكيميا الحاده فى الاونه الاخيره إلا إنه متوسط أعمار المرضى بهذا المرض مازال منخفض و هناك العديد من المؤشرات التى أرتبطت بهذا المرض منها : العمر، الهيئه العامه للفرد، عدد كرات الدم البيضاء،وجود تغير بالجينات الوراثيه .....إلخ

وجد أن حوالى 60% من مرضى الوكيميا الحاده لديه تغير فى الجينات الوراثيه و قد يكون هذا مؤشر للإستجابه للعلاج فى المستقبل أو غير ذلك و تبعا للتغيرات فى الجينات الوراثيه يمكن تقسيم المرضى إلى قليل الخطوره ،متوسط الخطوره وشديد الخطوره .

هناك العديد من الدراسات التى أكدت أن الالتصاق ما بين خلايا النخاع العظمى تساعد على حياة و تكاثر الخلايا الاوليه الخبيثه داخل وخارج النخاع .

هناك جزيئات هامه فى الالتصاق المبدئى المؤقت ما بين خلايا النخاع ولكن إثارة المستقبلات الكيميائيه بالمواد التى تفرز من الخلايا الاوليه فى الدم هى المسئوله عن تحويل هذا الالتصاق إلى إلتصاق قوى دائم .

وهناك ما يسمى بالعامل الأولى لخلايا النخاع العظمى يدعى cxcl 12 الذى يعمل بواسطة المستقبل cxcr4الذى له دور هام فى تكوين خلايا الدم وبناء الجهاز المناعى للجسم والحفاظ على هذه الخلايا داخل النخاع العظمى.

الهدف من المقال :

مراجعة ما نشر فى الدورات العلمية عن المستقبل الكيميائى الرابع فى مرضى اللوكيميا الميلوديه الحاده فى الدم وتوضيح أهمية أن يتم تقيمه فى جميع المرضى من البداية .

Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of diseases characterized by uncontrolled proliferation of myeloid progenitor cells. The AML is an aggressive malignancy with accumulation of blast cells in the bone marrow. ***(Mrozek, 2002)***.

Myeloblasts can invade the peripheral blood stream, and then localize in extramedullary sites. The regulation of this process has not been clearly explained so far. However, interactions between some chemokines and their specific receptors could be one of the mechanisms responsible for such kind of migration. ***(Matsunaga and Takemoto, 2003)***.

Despite major improvement in the understanding and treatment of certain leukemia during the past years, the overall survival (OS) of patients with (AML) remains poor, and new prognostic markers and therapeutic strategies are urgently needed. Several prognostic markers have been described in AML, including age, performance status, karyotype, white blood cell (WBC) count, serum lactate dehydrogenase (LDH), presence or absence of an antecedent hematologic disorder eg, myelodysplasia (MDS), and the presence of distinct cytogenetic abnormalities. Cytogenetic abnormalities can be detected in approximately 60% of AML patients and represent the most important predictor for response to therapy and relapse probability. Depending upon cytogenetic characteristics, patients can be classified into low-risk, intermediate-risk, or high-risk groups. ***(Konopleva, 2002)***.

However, there is substantial heterogeneity within these groups. About 35% to 50% of AML patients display a normal karyotype, which can further be subdivided using predictive molecular markers, such as mutations in the fetal liver

tyrosine kinase-3 (FLT3) gene and the mixed-lineage leukemia (MLL) gene ***(Dohner and Tobis, 2002)***.

Several studies indicated that adhesion to marrow stromal cells affects the survival and proliferation of AML cells and protects AML cells from chemotherapy in vitro and in vivo(***Konopleva, 2002)***.

Adhesion molecules, particularly the very late antigen-4 (VLA-4) and VLA-5 integrins, are considered essential for AML cell adhesion to respective stromal ligands (fibronectin) and for protection of AML cells from spontaneous or drug-induced apoptosis ***(Matsunaga and Takemoto, 2003)***.

However, adhesion molecules (selectins, integrins) alone are responsible only for initial, transient adhesion events; a second step triggered by chemokine receptor activation is necessary to transform reversible into firm adhesion and directional migration. ***(Frohling and Schlenk, 2002)***.

Stromal cell-derived factor-1 (SDF-1), which now is designated as CXCL12, is a homeostatic chemokine that is constitutively secreted by marrow stromal cells. CXCL12 signals through chemocine receptor 4 (CXCR4), which in turn plays an important role in hematopoiesis, development, and organization of the immune system. ***(Mrozek, 2002)***.

Chemotactic responsiveness of hematopoietic stem cells (HSCs) is restricted to CXCL12. This unique selectivity for CXCL12 may be necessary for retention of HSCs in the hematopoietic microenvironment and marrow-specific homing of circulating HSCs. ***(Frohling and Schlenk, 2002)***.

Rapid mobilization of HSCs by CXCR4 antagonists alone or in synergy with granulocyte colony-stimulating factor (G-CSF) has been demonstrated in clinical trials and supports

the hypothesis that CXCL12 is essential for HSC retention within the marrow. Prognostic impact of CXCR4 expression levels on the neoplastic cells has been demonstrated in breast cancer and renal cell cancer ***(Dohner and Tobis, 2002)***.

Aim of the study:

Review of literature of cxcr4 in AML and suggest that cxcr4 should be incorporated as prognostic factor in AML patients.

Introduction

Bone marrow

Bone marrow is the soft inner part of some bones such as the skull, shoulder blades, ribs, pelvis, and backbones. The bone marrow is made up of a small number of blood stem cells, more mature blood-forming cells, fat cells, and supporting tissues that help cells grow ***(Ron, 2004)***

Blood stem cells go through a series of changes to make new blood cells. During this process, the cells develop into either lymphocytes (a kind of white blood cell) or other blood-forming cells. The other blood-forming cells can develop into 1 of the 3 main types of blood cell components; red blood cells, white blood cells (other than lymphocytes) and platelets ***(Birch, 1996)***

Red blood cells

Red blood cells carry oxygen from the lungs to all other tissues in the body, and take carbon dioxide back to the lungs to be removed. Anemia (having too few red blood cells in the body) typically causes a person to feel tired, weak, and short of breath because the body tissues are not getting enough oxygen ***(Bloomfield, 2007)***.

Platelets

Platelets are actually cell fragments made by a type of bone marrow cell called the megakaryocyte. Platelets are important in plugging up holes in blood vessels caused by cuts or bruises. A shortage of platelets is called thrombocytopenia. A person with thrombocytopenia may bleed and bruise easily ***(Baldus, 2007)***.

White blood cells

White blood cells help the body fight infections. Lymphocytes are one type of white blood cell. The other types of white blood cells are granulocytes (neutrophils, basophils, and eosinophils) and monocytes. ***(Mrozek, 2002).***

Lymphocytes:

These are the main cells that make up lymphoid tissue, a major part of the immune system. Lymphoid tissue is found in lymph nodes, the thymus gland, the spleen, the tonsils and adenoids, and is scattered throughout the digestive and respiratory systems and the bone marrow. ***(Marcucci and Ruppert, 2006)***.

Lymphocytes develop from cells called lymphoblasts to become mature, infection-fighting cells. The 2 main types of lymphocytes are known as B lymphocytes (B cells) and T lymphocytes (T cells):

B lymphocytes protect the body from invading germs by developing (maturing) into plasma cells, which make proteins called antibodies. The antibodies attach to the germs (bacteria, viruses, and fungi), which helps other white blood cells to recognize and destroy them. T lymphocytes can recognize cells infected by viruses and directly destroy these cells. ***(Mrozek, 2002)***.

Granulocytes:

These are white blood cells that have granules in them, which are spots that can be seen under the microscope. These granules contain enzymes and other substances that can destroy germs, such as bacteria. The 3 types of granulocytes -- neutrophils, basophils, and eosinophils -- are distinguished by the size and color of their granules. Granulocytes develop from