Detection of Minimal Residual Disease in Acute Leukemia

Essay

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By:

Sameh Omara

M.B.B.Ch, Ain shams University

Supervised by

Dr. Hoda Ahmed Gad Allah

Professor of Internal Medicine and Clinical Hematology
Faculty of Medicine, Ain Shams University

Dr. Hany Hegab

Assistant Professor of Internal Medicine and Clinical Hematology
Faculty of Medicine, Ain Shams University

Dr. Walaa Ali El Salakawy

Lecturer of Internal Medicine and Clinical Hematology
Faculty of Medicine, Ain shams University

Faculty of Medicine
Ain Shams University
٢٠١٣


بسم الله الرحمن الرحيم
قالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ
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Sameh Omara

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List of Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
ASH	American society of hematology
BM	Bone marrow
CBF	Core binding factor
CCR	Complete clinical remission
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CN-AML	Cytogenetically normal acute myeloid leukemia
CR	Complete remission
DFS	Disease free survival
DIC	Dessimenated intravascular coagulopathy
FISH	Fluorescence in situ Hybridization:
F-RK	Favorable risk karyotayping
HSCT	Hematopoetic stem cell transplantation
I-RK	Intermediate risk karyotyping
LAIPS	Leukemia associated immunophenotypes
MDS	Myelodysplastic syndrome
MLL	Mixed lineage leukemia
MRD	Minimal residual disease
OS	Overall survival
PB	Peripheral blood
PCR	Polymerase chain reaction
RQ-PCR	Real time quantitative Polymerase chain reaction
U-RK	Unfavorable risk karyotyping

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Introduction

Minimal residual disease(MRD) is the name given, to small numbers of leukemic cells that remain in patients during treatment or after when the patient is morphologically in remission ,it is the major cause of relapse in leukemia. The tests used to assess/ detect leukemic cell were not sensitive enough to detect MRD. Recently, very senstive molecular biology tests are available- based on DNA , RNA or PROTEINS -and these can measure minute level of malignant cells in tissue samples as low as one malignant cell in million normal cells. ***(Frie et al., ٢٠٠٣).***

In cancer treatment particulary leukemia, MRD testing has several important roles: determining whether the treatment has eradicated the cancer or whether traces remain , comparing the efficacy of different regimens of treatment, monitoring the patient remission status and recurrence or relapse of leukemia and choosing the optimal therapy for treatment.***(Haferlach , ٢٠٠٨).***

The tests are not simple, are often a part of research or trials, and some have been accepted for routine clinical use. The common principle underlying all MRD assays is that the leukemogenic process has resulted in molecular and cellular changes that distinguish leukemic cells from their normal

counterparts ***(Szczepanski al., ٢٠٠١; Campana, ٢٠٠٣).*** These leukemia - associated features are identified at diagnosis or at relapse and then used to monitor MRD.

One of the distinguishing features of leukemic cells is the expression of cell markers in abnormal patterns.These abnormal cell profiles are best detected with multiparameters flow cytometry ***(Campana, ٢٠٠٣).***

A second distinguishing feature of leukemic cells is clonal rearrangement of the genes encoding immunoglobulins and T- cell receptors (TCR) proteins .These leukemia-specific molecular signatures can be found in the majority of cases of acute lymphoblastic leukemia ***(Pongers-Willemse al., ١٩٩٩)***.

But in less than ١٠٪ of acute myeloid leukemia.`Real-time´ polymerase chain reaction (PCR) is the preferred method for the detection of cells with such rearrangement ***(van der Valden al., ٢٠٠٣).***

A third leukemia associated feature can be used to distinguish leukemia from normal cells is presented by chromosomal abnormalities and resulting gene fusions,real time PCR provides the most accurate way to measure their levels ***(Gabert al., ٢٠٠٣).***

Aim of the Work

Review of the recent advances regarding the detection of minimal residual disease in acute leukemia.

Introduction and Rationale of Minimal Residual Disease

Introduction:

Patients with acute lymphoblastic or acute myeloid leukemia may harbor up to 10^{12} malignant cells at presentation. With chemotherapy, the majority of both children and adults achieve complete clinical remission (CCR) following the first course of induction therapy. However, even in CCR, patients can still have as many as 10^{10} malignant cells in the marrow, and this is responsible for relapse in ١٥-٢٠٪ of children and ٥٠-٦٠٪ of adults with acute lymphoblastic leukemia (ALL) and in a varying proportion of patients with acute myeloid leukemia (AML).

A variety of methods have been developed to detect malignant cells in patients in CCR, i.e. to detect 'minimal residual disease' with higher sensitivity than morphological method. This conventionally defines CCR by the presence of less than ٥٪ blasts in the bone marrow.The goal of more sensitive techniques for MRD detection is to adjust patients' therapy in order to reduce both the risk of relapse and of overtreatment, particularly in children. ***(Campana D, ٢٠٠٩).***

Definition of MRD ;

Minimal residual disease (MRD) is defined as the lowest level of disease detectable in patients in complete clinical remission (CCR) by the methods available (morphological remission). A reliable technique for MRD detection should be specific (discriminate malignant from normal cells), sensitive (able to detect up to one leukemic cell in at least ١٠٠ normal cells), reproducible (widely applicable in different laboratories)and quantitative (provide a numerical estimate of positive cells).

Submorphologic (ie, minimal) residual disease (MRD) can be monitored in virtually all children and adolescents with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) using methods such as flowcytometric detection of leukemic immunophenotypes or polymerase chain reaction amplification of fusion transcripts, gene mutations, and clonal rearrangements of antigen-receptor genes. Numerous studies have demonstrated the clinical importance of measuring MRD, spurring the design of clinical trials in which MRD is used for risk assignment and treatment selection.

Rationale For Minimal Residual Disease Testing :

Monitoring response to treatment by periodic examination of bone marrow aspirates is an integral part of the clinical management of patients with acute leukaemia. The presence of residual leukaemia and the overall status on normal haematopoiesis, as determined by the cellular appearance of bone marrow smears, provide an indication of the sensitivity of leukaemic cells to chemotherapy and of the degree of haematopoietic regeneration occurring during treatment intervals. Because the morphology of leukaemic cells generally resembles that of normal lympho-haematopoietic progenitors, it is difficult to identify leukaemic cells with confidence. In fact, identification of individual leukaemic cells scattered among normal bone marrow cells might not be possible even for an experienced haemopathologist**. (*Campana D, ٢٠٠٩).***