

Minimal Residual Disease Assessment by Flow Cytometry in B-lineage Acute Lymphoblastic Leukemia to Assess Response to Treatment and Impact on Outcome

Thesis

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List of abbreviation

ABL: Abelson murine leukemia
A-CGH: array-comparative genomic hybridization
ALL: acute lymphoblastic leukemia
ALLO-SCT: allogenic stem cell transplantation
AML: acute myeloid leukemia
ASO: allele-specific oligonucleotide
BCP: B cell precursor
BCR: B-cell receptor
BCR: breakpoint cluster region
BFM: Berlin-Frankfurt-Münster Group
CALGB: cancer and leukemia group B
CAR: Chimeric antigen receptor
CCR: continuous complete remission
CIR: cumulative incidence of relapse
CMR: complete molecular remission
CNS: central nervous system
COG: children oncology group
CR: complete remission
CRLF2: cytokine receptor-like factor 2
CRS: cytokine release syndrome
CTLA-4: cytotoxic T lymphocyte antigen-4
DFS: disease free survival
DIC: disseminated intravascular coagulation
EFS: event free survival
FISH: fluorescence in situ hybridization

GIMEMA: Gruppo Italiano Malattie EMatologiche dell'Adulto
GMALL: German multicenter acute lymphoblastic leukemia
GRAALL: French Group for Research on Adult ALL
GVHD: graft versus host disease
GVL: graft versus leukemia
HR: high risk
HSCT: hematopoietic stem cell transplantation
HTS: high-throughput sequencing
IPT: immunophenotyping
K–M: Kaplan Meier
LFS: leukemia free survival
MAC: myeloablative conditioning
MDACC: MD Anderson Cancer Center
MFC: multiparametric flow cytometry
MPO: myeloperoxidase
MRD: minimal residual disease
MSD: matched sibling donors
NGS: Next-Generation Sequencing
NILG: Northern Italian Study Group
NRM: non-relapse mortality
NSE: nonspecific esterase
OS: overall survival
PALG: Polish Adult Leukemia Group
PAS: Periodic acid-Schiff
PD-1: programmed cell death-1
PETHEMA: Spanish Programa Español de Tratamientos en Hematologia
PFS: progression-free survival
RFS: relapse free survival

RI: relapse incidence

RIC: reduced intensity conditioning

RR: relapse rate

RT-qPCR: real time quantitative polymerase chain reaction

SBB: Sudan black B

SNP: single nucleotide polymorphisms

SR: standard risk

TCP: T-cell precursor

TKI: tyrosine kinase inhibitors

TLC: total leucocytic count

URD: unrelated donors

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Abstract

The prognostic value of minimal residual disease (MRD) assessed by multi-parameter flow cytometry (MFC) was investigated among 56 adult patients with B-cell acute lymphoblastic leukaemia (B-ALL) treated between 2014 and 2018 using regimens including the Dana Farber and Hoelzer protocols. In this study, 44 (78.6%) achieved complete remission (CR) with a relapse rate of 38.6% (17 cases out of 44 cases) after a median follow up of 15 months. median age was 29.5 years (range 18 to 60). Median white blood cell count (WBC) was 17.75×10^3 (range, $0.38-340 \times 10^3/\mu\text{l}$). MRD by MFC was assessed with a sensitivity of 0.01%, using a 7 marker, 4-colour panel on bone marrow specimens obtained at D14, D28 and post consolidation. MRD ≤ 0.01 at D14 was associated with improved disease-free survival (DFS) and overall survival (OS) ($P < 0.001$ and $P < 0.001$ respectively). Similarly MRD ≤ 0.01 at D28 and undetectable levels post consolidation was associated with improved DFS ($P < 0.001$ and $P < 0.001$ respectively) and OS ($P < 0.001$ and $P < 0.001$ respectively). Multivariate analysis including age, WBC at presentation, IPT, cytogenetics, treatment protocol and MRD status at D14, D28 and post consolidation, indicated that MRD negative status was an independent predictor of DFS. Achievement of an MRD negative state assessed by MFC is an important predictor of DFS and OS in adult patients with ALL.

Keyword: acute lymphoblastic leukemia, minimal residual disease.