

TARGETED THERAPY FOR HEMATOLOGICAL MALIGNANCIES

(Essay)

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Abstract

Leukemias and lymphomas are relatively common, affect all ages and demonstrate extra-ordinary biologic, morphologic and clinical heterogeneity. Immunotherapy, mainly antibody-based therapy in non-Hodgkin's lymphomas, has become one of the success stories of targeted therapy today especially rituximab which is in broad clinical use all over the world. The combination with chemotherapy increases remission rates and remission duration. The primary advantage of using T cells for adoptive therapy is their ability to specifically target tumor cells through the recognition of differentially expressed tumor proteins presented on the cell surface.

The story of imatinib, a tyrosine kinase inhibitor, is one of the first examples of a successful targeted therapy in hematological malignancies. The development of second and third generations of tyrosine kinase inhibitors was necessary in resistant cases. A number of receptor tyrosine kinase inhibitors are being used in hematologic malignancies to block angiogenesis through vascular endothelial growth factor (VEGF) inhibition.

Emerging knowledge about molecular mechanism of apoptosis dysregulation in leukemia has revealed a plethora of potential drug discovery targets as well as for inhibitors of DNA methylation. Initial treatment with azacitidine or decitabine, followed by histone deacetylases inhibitors, can produce additive or synergistic effects for re-expression of transcriptionally silenced genes having clinical benefit in patients with AML and MDS.

Key words: •Leukemia •Lymphoma •Monoclonal antibodies •Tyrosine kinase inhibitor •Methylation •Apoptosis

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List of Abbreviations

¹³¹ I	Iodine-131
¹⁸⁸ Re	Rhenium -188
²¹¹ At	Astatine 211
²¹³ Bi	Bismuth -213
²²⁵ Ac	Actinium 225
⁹⁰ Y	Yttrium-90
ABL	Abelson
aCML	Atypical CML
ADCC	Antibody dependant cell mediated cytotoxicity
Ag	Antigen
AITL	Angioimmunoblastic T cell lymphoma
AK	Aurora kinase
AKT	A serine/threonine kinase
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AML1	Acute myeloid leukemia gene1
AMM	Asymptomatic multiple myeloma
AMML	Acute myelomonocytic leukemia
AP	Accelerated phase
Apaf1	Apoptotic protease-activating factor 1

APC	Antigen presenting cell
APL	Acute promyelocytic leukemia
APO-2	Apoptosis 2 receptor
ARG	ABL-related gene product
ATLL	Adult T-cell leukemia/lymphoma
ATP	Adenosine triphosphate
ATRA	All trans-retinoic acid
BAK	BCL-2 killer (antagonist)
BC	Blastic crisis
BCL2	B cell lymphoma/ leukemia 2
Bcl _x	Bcl-2 related gene x
BCL _{xl}	Long form of Bcl _x
BCR	Breakpoint cluster region of chromosome 22
bFGF	Basic fibroblast growth factor
BL	Burkitt's lymphoma
BM	Bone marrow
BMCs	Bone marrow stem cells
BMP	Bone morphogenetic proteins
BMT	Bone marrow transplant
cAMP	Cyclic adenosine monophosphate
CARDs	Caspase recruitment domains
Caspases	Cysteine – aspartate residues
CBC	Complete blood count
CBF	Core binding factor

CCR	Complete cytogenetic remission
CD	Cluster of differentiation
CDRs	Complementarity determining regions
CEL	Chronic eosinophilic leukemia
CHOP	Cyclophosphamide/ adriamycine/ oncovin/ prednisone
CHR	Complete hematological response
ChTCR	Chimeric T cell receptor
cKIT	Cellular homologue of the viral kit oncogene
CLL	Chronic lymphatic leukemia
CMI	Cell mediated immunity
CML	Chronic myeloid leukemia
CML-BP	CML-blastic phase
CMML	Chronic myelomonocytic leukemia
CMPD	Chronic myeloproliferative disease
CMR	Complete molecular remission
CMV	Cytomegalovirus
C-myc	Cellular myc oncogene
CNL	Chronic neutrophilic leukemia
CNS	Central nervous system
CP	Chronic phase
CPG	Cytidylyl 2p5p phosphoryl guanosine
CPK	Creatinine phosphokinase
CR	Complete remission
CT	Combination chemotherapy

CTCL	Cutaneous T cell lymphoma
CTLs	Cytotoxic T lymphocytes
Cytc	Cytochrome c
D	Day
DCs	Dendritic cells
DD	Death domain
DED	Death effector domain
D-HPLC	Denaturing high performance liquid chromatography
DIC	Disseminated intravascular coagulation
DISC	Death inducing signaling complex
DLCL	Diffuse large cell lymphoma
DNA	Deoxyribonucleic acid
DNMTs	DNA methyl transferases
ds RNA	Double stranded ribonucleic acid
DT	Diphtheria toxin
EBV	Epstein-Barr virus
ECM	Endothelial cell mediated
EGF	Epidermal growth factor
EGIL	European group for the immunological classification of leukemia
ELISA	Enzyme linked immunosorbant assay
ETO	Eight twenty one gene
ETV6	Ets variant gene 6
FAB	French –American –British group

Fab	Fragment antibody binding
FACS	Fluorescence activated cell sorting
FADD	Fas associating protein with death domain
FasL	Fas ligand
Fc-R	Fragment c receptors
FCR γ	Fragment crystalline receptor gamma
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FGFR	Fibroblast growth factor receptor
FIP1L1	Fip1 like 1
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FLICE	Fas- associating protein with death domain like IL1-converting enzyme
FLIPI	Follicular lymphoma international prognostic index
Flk	Fetal liver kinase
FLT3	Fms like tyrosine kinase 3
FND	Fludarabine/ Mitoxantrone/ Dexamethasone
Fr C	Fragment C
G1	Gap phase-1 between cell division and DNA synthesis
G-CSF	Granulocyte colony stimulating factor
GDEPT	Gene directed enzyme pro-drug therapy
GIST	Gastro-intestinal stromal cell tumor
GM-CSF	Granulocyte macrophage colony stimulating factor

GMP	Good manufacturing practice
Go	Cell resting phase
GO	Gemtuzumab ozogamicin
GVHD	Graft versus host disease
GVL	Graft versus leukemia
h	Hour
HAMA	Human murine antibodies
Hb	Hemoglobin
HCL	Hairy cell leukemia
HDACs	Histone deacetylases
HES	Hypereosinophilic syndrome
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HLA	Human leucocytic antigen
HMCL	Human myeloma cell line
HSC	Human stem cell
HSCT	Human stem cell transplantation
HTLV	Human T lymphotropic virus
IC ₅₀	Inhibitory concentration of 50%
ICAM	Intracellular adhesion molecule
ID	Intradermal
Id	Idiotype
Ig	Immunoglobulin

Ig H	Immunoglobulin H
Ig V _H	Immunoglobulin variable region heavy chain gene
IGF- 1	Insulin like growth factor -1
IL	Interleukin
IL-1b	Interleukin 1 beta
IL2R	IL-2 receptor
IM	Intramuscular
INF γ	Interferon gamma
IRIS	International Randomized INF versus STI 571
IT	Immunotherapy
ITD	Internal tandem duplications
IV	Intravenous
I κ B	Inhibitor of nuclear factor- κ B
JAK	Janus kinase
JMML	Juvenile myelomonocytic leukemia
JNK	Jun NH2- terminal kinase
KDa	Kilodalton
KDR	Kinase domain region
LBL	Lymphoblastic lymphoma/ leukemia
LCH	Langerhans' cell histiocytosis
LCL	Large cell lymphoma
LDH	Lactate dehydrogenase
LFT	Liver function test
LGLL	Large granular lymphocytic leukemia