TARGETED THERAPY FOR HEMATOLOGIC MALIGNANCIES

An Essay

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بسم الله الرحمن الرحيم

(قَالُوا سُبْحَانَكَ لا عِلْمَ
لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ
أَنْتَ الْعَلِيمُ الْحَكِيمُ)

(سورة البقرة:٣٢)

Dedication

My work is dedicated to:

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Gamil Mohamed Ali

List of Abbreviations

ADCC	Antibody dependent cellular cytotoxicity
ADP	Adenosine di phosphate
ALK	anaplastic lymphoma kinase
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
AMP	Adenosine mono phosphate
APCs	antigen-presenting cells
APL	acute promyelocytic leukemia
Ara-C	Cytarabine
ASCT	autologous stem cell transplantation
ATO	arsenic trioxide
ATP	Adenosine tri phosphate
ATRA	all-trans- retinoic acid
CALGB	Cancer and Leukemia Group B
CBF	core binding factor
CBF-AML	core binding factor leukemias
CCyR	complete cytogenetic response
CD	Cluster differentiation
CDC	Complement-dependent cytotoxicity
CDK	cyclin-dependent kinase
CDKI	cyclin-dependent kinase inhibitor
CDR	complementarity-determining regions
CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia
CMV	cytomegalovirus

COX-2	Cyclooxygenase-2
CR	complete response
CRu	CR unconfirmed
CSF-I	colony-stimulating growth factor I
DNA	Deoxyribonucleic acid
DNMTi	DNA Methyl Transferase Inhibitor
DOR	duration of response
EGF	epidermal growth factor
Erk	The Ras/Raf/extracellular signal-regulated kinase
FGF	fibroblastic growth factor
FKHR	Forkhead
FltL	FLT3 ligand
FL	follicular lymphoma
FLT3	Fms-like tyrosine kinase 3
FLT3R	FMS-like tyrosine kinase 3 receptor
FTIs	farnesyltransferase inhibitors
G-CSF	granulocyte colony-stimulating factor
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GM-CSF	granulocyte macrophage colony-stimulating factor
GO	Gemtuzumab ozogamicin
Grb2	growth factor receptor binding protein 2
GSK-3	glycogen synthase kinase-3
GSK-3β	glycogen synthase kinase-3β
GST	Glutathion-S-transferase
GTP	Guaninosine tri phosphate
GvHD	graft-versus-host disease
HDAC	Histone deacetylase

HL	Hodgkin lymphoma
HLA	human leukocyte antigen
HUS	hemolytic-uremic syndrome
IAP	inhibitor of apoptotic pathway
Id	idiotype
IFN	Interferon
IFP	interstitial fluid pressure
Ig	Immunoglobulin
IGF-I	insulin-like growth factor I
IGF-IR	insulin-like growth factor receptor I
IGFs	insulin-like growth factors
IkB	inhibitor of nuclear factor-kB
IL	interleukin
IR	insulin receptor
IRS	insulin receptor substrates
ITDs	internal tandem duplications
Jak	janus kinase
JNK	c-Jun NH2-terminal kinase
mAbs	monoclonal antibodies
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
MEK	mitogen-activated protein/extracellular signal-regulated kinase
MMAE	monomethyl auristatin E
MMP	Matrix Metalloproteinases
MMR	major molecular response
MR	minimal response
MRD	minimal residual disease

mRNA	Messenger ribonucleic acid
mTOR	mammalian target of rapamycin
MZL	marginal-zone lymphoma
nCR	near-CR
NFkB	nuclear factor k B
NHL	Non hodjkin lymphoma
NPM	nucleophosmin
NSCLC	Non Small Cell Lung Cancer
Ontak	Denileukin diftitox
OR	overall response
ORR	Overall response rate
OS	overall survival
PDGF	platelet derived growth factor
PDGFR	platelet-derived growth factor receptor
PDK1	phosphoinositide-dependent kinase 1
PFS	progression-free survival
Ph	Philadelphia
PI3K	phosphatidylinositol 3-kinase
PIAS	protein inhibitor of activated stat
PKB	protein kinase B
PKC	Protein kinase C
PN	peripheral neuropathy
PR	partial response
PRIMA	The European International Primary Rituximab and Maintenance
PTB	phosphotyrosine-binding
RAR	retinoic acid recepto
Rb	retinoblastoma

Rheb	Ras homologue enriched in the brain
RIT	Radioimmunotherapy
RNA	Ribonucleic acid
RR	rituximab-resistant
RSK	ribosomal S6 kinase
RTK	receptor tyrosine kinase
RT-PCR	Reverse transcriptase polymerase chain reaction
RXR	retinoid X receptors
S6K	ribosomal protein S6 kinase
SAHA	suberoylanilide hydroxamic acid
SAPK	stress-activated protein kinase
SCF	stem cell factor
SD	stable disease
SH2	Src homology-2
Shc	Src-homology collagen protein
SHIP	SH2-domain-containing inositol phosphatase
SHP-1	SH-2 domain containing protein tyrosine phosphatase-1
SHP2	SH2-domain-containing protein tyrosine phosphatase 2
SLL	small lymphocytic lymphoma
SOCS	suppressor of cytokine signaling
SOS	Son of Sevenless
Stat	signal transducer and activator of transcription
TK	tyrosine kinase
TNF	tumor necrosis factor
TSA	trichostatin A
TSC1, TSC2	tuberous sclerosis complexes 1 and 2
TSP-1	thrombospondin-1

TTP	time-to-progression
TTR	time-to-response
VEGF	vascular endothelial growth factor
VPA	valproic acid
XIAP	X-linked inhibitor of apoptosis
4E-BP	4E-binding protein

Contents

INTRODUCTION

Conventional cytotoxic therapy of hematologic malignancies is often associated with significant morbidity. This morbidity is often due to the lack of specificity for hematopoietic cells. Therefore, the concept of targeted therapy for patients with hematologic malignancies has received attention for many years. The goal of targeted therapy is to target specific malignant cells, while sparing normal cells and tissues **(Athena et al., 2002).**

Though all cancer treatments (including surgery, radiation, and cytotoxic chemotherapy) could be considered as therapy targeted against cancer, the term targeted therapy is more narrowly defined as the use of directed immunotherapy or molecularly directed therapy **(Kuriakose, 2005).**

The concept of targeted therapy for patients with cancer has intrigued researches for years. In 1953, **Pressman and Korngold** showed that antibodies could specifically target tumor cells. Unfortunately, it was not until 1975, when **Kohler and Milstein** described their Nobel Prize-winning work in hybridoma technology, that a continuous supply of monoclonal antibodies (mAbs) that targeted specific antigens became available. By 1979, **Nadler et al.** treated the first patient with mAb therapy **(Nadler et al., 1980).**

In general, there are three main classes of cytotoxic mAbs that have been developed. The first consists of unconjugated mAbs, where the antibody itself mediates cell killing. The remaining two classes involve mAbs that are conjugated to either a potent drug/toxin, or a radioisotope **(Athena et al., 2002).**

In addition to the advances with mAbs therapy, molecular targeting of hematologic malignancies, primarily chronic myelogenous leukemia (CML), through specific tyrosine kinase inhibitors has been developed **(Druker et al., 2001)**.

Despite the progress that has been made with developing targeted therapies, there are numerous obstacles to successful therapy **(Athena et al., 2002).**

AIM OF THE WORK

The aim of this work is to review different modalities, advantages and disadvantages of targeted therapy in hematologic malignancies which became in the forefront of ongoing researches in the new era.

TARGETED THERAPY

What is targeted therapy?

Targeted therapy is defined as a drug or molecule causing tumor cell death by interacting with predefined target(s) present on malignant cells **(Mishra and Parikh, 2006).** It is a treatment that aims to target some biologic feature of the tumor to eradicate it **(Oeffinger et al., 2006).** Though all cancer treatments (including surgery, radiation, and cytotoxic chemotherapy) could be considered as therapy targeted against cancer, the term targeted therapy is more narrowly defined as the use of directed immunotherapy or molecularly directed therapy **(Kuriakose, 2005).**

At its simplest, targeted therapy implies a therapy with a specific molecular target. This is a very low-level definition because any therapy that works must have a molecular target. In some cases (trastuzumab), the target was discoved first, while in others (aspirin), the drug was discoved before the target **(George and Sledge, 2005).**

In a related way, with targeted therapy, does it mean that the therapy has only one target? Some targeted therapies (eg, imatinib) have more than one molecular target, so one cannot even claim that targeted therapy requires an exacting degree of specificity **(Druker et al., 2004).** So the simple equation, "drug + molecular target = targeted therapy," is essentially meaningless. At best, it can be considered necessary but not sufficient **(George and Sledge, 2005)**

A targeted therapy should attack a biologically important process (usually, though not necessarily, a single molecule), preferably one central to a hallmark of cancer. The target should be measurable in the clinic, and measurement of the target (in either quantitative or qualitative terms) should correlate with clinical outcome when the targeted therapy is

administered. Using this approach, gefitinib moved into the club of targeted therapy only in the clinic. That is to say, its inclusion in the targeted therapy club required the discovery of epidermal growth factor mutations correlating with therapeutic outcome (**Lynch et al., 2004)**. Similarly, it is reasonable to suggest that agents targeting vascular endothelial growth factor do not yet pass the club of targeted therapy. It is not currently possible to measure a target correlating treatment with outcome. It is not even certain at present whether the cells being attacked are endothelial cells, cancer cells, or both **(Schneider and Miller. 2005)**

Indeed, if what is said regarding a definition of targeted therapy is correct, it is premature to consider a therapy functionally targeted unless, and until, large positive studies become available **(George and Sledge, 2005).**

Historical background:

The concept of targeted therapy for patients with cancer has intrigued researches for years. In 1953, **Pressman and Korngold** showed that antibodies could specifically target tumor cells**.** Unfortunately, it was not until 1975, when **Kohler and Milstein** described their Nobel Prize-winning work in hybridoma technology, that a continuous supply of monoclonal antibodies (mAbs) that targeted specific antigens became available**.** By 1979, **Nadler et al**. treated the first patient with mAb therapy **(Nadler et al., 1980).**

Why targeted therapy?

Conventional therapy has the following limitations:

1) Conventional therapy is not specific to a particular tumor type and acts by killing rapidly dividing cells regardless of whether or not they are malignant **(Oeffinger et al., 2006).**