International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319 – 6505, Impact Factor: SJIF: 5.995
Available Online at www.journalijcar.org
Volume 6; Issue 8; August 2017; Page No. 5502-5508
DOI: http://dx.doi.org/10.24327/ijcar.2017.5508.0739

Research Article

OVERVIEW OF MOLECULAR TARGETED THERAPY IN CANCER

Sahil Gupta*., Ankit Batra., Siddararth Kumar and Pranay Katepogu

King George's Medical University

ARTICLE INFO

Article History:

Received 15th May, 2017
Received in revised form 12th June, 2017 Accepted 10th July, 2017
Published online 28th August, 2017

Key words:

Molecular, Targeted Chemotherapy, Cancer

ABSTRACT

Systemic therapy of cancer by cytotoxic agents is the cornerstone of cancer treatment. But now, these agents are being supplemented by a new generation of drugs that recognize specific targets in or on the cancer cells.These targeted agents can be classified broadly into monoclonal antibodies, signal pathway inhibitors and those targeting genetic abnormalities. Gene therapy and immunotherapy are the latest weapons in the arsenal that have been introduced and studies are ongoing. Although there as been an explosion in the armamentarium against cancer as far as targeted therapy in concerned, we need to further intensify our efforts as the era of 'personalised medicine' dawns on us and the concept of quality of life becomes more relevant in a developing country like ours.

INTRODUCTION

Systemic therapy of cancer by cytotoxic agents is the cornerstone of cancer treatment. But now, these agents are being supplemented by a new generation of drugs that recognize specific targets in or on the cancer cells. These newer generation drugs not only fight cancer "smartly" but with fewer side effects as they tend to be more specific. For this reason, it is a promising therapy for the 3rd millennium[(1)]. Traditional cytotoxic chemotherapy works primarily through the inhibition of cell division. In addition to cancer cells, other rapidly dividing cells (e.g. hair, gastrointestinal epithelium, bone marrow etc.) are affected by these drugs. These molecular drugs are in their infancy; however, they hold promise of more effective therapies with fewer side effects. Several targeted drugs are already approved by the US Food and Drug Administration (FDA) for use in malignancies, and several more are in various phases of clinical developments[(2)]. The conventional anticancer agents used as systemic agents not only kill the rapidly proliferating cancer cells but they also lethal to all fast proliferating tissues in the body. The conventional therapy is going to stay for a longer period of time, however, it is deemed to be supplemented by targeted therapies[(3)].

These targeted agents can be classified broadly into monoclonal antibodies, signal pathway inhibitors and those targeting genetic abnormalities.

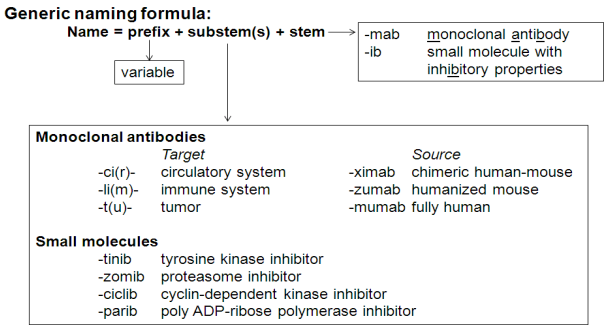
Corresponding author:* **Sahil Gupta
King George's Medical University

Below is a brief description of targeted agents that have been approved by the USFDA for use in the treatment of cancer during the last several years.

Monoclonal Antibodies- They are immunoglobulin structures designed to target specific antigens found on the cell surface, such as transmembrane receptors or extracellular growth factors for attack. In some cases, monoclonal antibodies are conjugated to radio-isotopes or toxins to allow specific delivery of these cytotoxic agents to the intended cancer cell target. Monoclonal antibodies end with the stem "-mab" (monoclonal antibody). Monoclonal antibodies have an additional subsystem designating the source of the compound e.g., "-ximab" for chimeric human-mouse antibodies, "-zumab" for humanized mouse antibodies, and "-mumab" for fully human antibodies [(4)].

Small Molecules/Signal Pathway Inhibitors - Small molecules are usually designed to interfere with the enzymatic activity of the target protein. They can penetrate the cell membrane to interact with targets inside a cancer cell. Small molecules end with the stem "-ib" (indicating that the agent has protein inhibitory properties).

Both monoclonal antibodies and small molecules contain an additional stem in the middle of the name describing the molecule's target; examples for monoclonal antibodies include "-ci-" for a circulatory system target and "-tu-" for a tumor target, while examples for small molecules include "-tin-" for tyrosine kinase inhibitors and "-zom-" for proteasome inhibitors. At the beginning of the generic name there is a prefix that is unique for each agent [(4)].



Gene Therapy - Gene therapy implies any procedure intended to treator alleviate a disease by genetically modifying the cell of a patient either by blocking the expression of the oncogene or by replacing the missing or defective tumor suppressor gene. The material to be transferred into patientcells may be genes, gene segments, or oligonucleotides. Gene therapy can be broadly broken down into three categories- immunotherapy, oncolytic virotherapy and gene transfer [(5)]. We have enlisted and briefly described the above mentioned modalities with the agents that have been approved by the USFDA during the past several years.

Table 1

Drug	Target	Indication	Year of approval
Ado-trastuzumab emtansine (Kadcyla)	HER2 (ERB-B2/neu)	• Breast cancer (HER2+)	2013
Alemtuzumab (Campath)	CD52	• B-cell CLL	2001
Atezolizumab (Tecentriq)	PD-L1	• Urothelial carcinoma • Non-small cell lung cancer	2016
Belimumab (Benlysta)	BAFF	• Lupus erythematosus	2011
Bevacizumab (Avastin)	VEGF ligand	• Cervical cancer • Colorectal cancer • Fallopian tube cancer • Glioblastoma • Non-small cell lung cancer • Ovarian cancer • Peritoneal cancer • Renal cell carcinoma	2014 2013 2014 2009 2006 2014 2014 2009
Brentuximab vedotin (Adcetris)	CD30	o Hodgkin lymphoma o Anaplastic large cell lymphoma	2011 2011
Canakinumab (Ilaris)	IL-1β	• Juvenile idiopathic arthritis • Cryopyrin-associated periodic syndromes	2016 2016
Cetuximab (Erbitux)	EGFR (HER1/ERB-B1)	• Colorectal cancer (KRAS wild type) • Squamous cell cancer of the head and neck	2004 2004
Daratumumab (Darzalex)	CD38	• Multiple myeloma	2015
Denosumab (Xgeva)	RANKL	• Giant cell tumor of the bone • Bone metastasis • Increase bone mass in patients on AI/ADT • Postmenopausal women with osteoporosis at high risk of fracture	2013 2010 2011 2010
Dinutuximab (Unituxin)	B4GALNT1 (GD2)	• Paediatric neuroblastoma	2015
Elotuzumab (Empliciti)	SLAMF7 (CS1/CD319/CRACC)	• Multiple myeloma	2015
Gemtuzumab ozagamycin (pfizer)	CD33	• AML	2010
Ibritumomab tiuxetan (Zevalin)	CD20	• Non-Hodgkin's lymphoma	2002
Ipilimumab (Yervoy)	CTLA-4	• Melanoma	2011
Necitumumab (Portrazza)	EGFR (HER1/ERBB1)	• Squamous non-small cell lung cancer	2015
Nivolumab (Opdivo)	PD-1	• Hodgkin lymphoma • Melanoma • Non-small cell lung cancer • Renal cell carcinoma • Head and neck cancer	2016 2014 2015 2015 2016
Obinutuzumab (Gazyva)	CD20	• Chronic lymphocytic leukaemia • Follicular lymphoma	2013 2016
Ofatumumab (Arzerra, HuMax-CD20)	CD20	• Chronic lymphocytic leukaemia	2016
Olaratumab (Lartruvo)	PDGFRα	• Soft tissue sarcoma	2016
Panitumumab (Vectibix)	EGFR (HER1/ERBB1)	• Colorectal cancer (KRAS wild type)	2006
Pembrolizumab (Keytruda)	PD-1	• Melanoma • Non-small cell lung cancer (PD-L1+) • Head and neck squamous cell carcinoma	2014 2015 2016
Pertuzumab (Perjeta)	HER2 (ERBB2/neu)	• Breast cancer (HER2+)	2013
Ramucirumab (Cyramza)	VEGFR2	• Colorectal cancer • Gastric cancer or Gastroesophageal junction (GEJ) adenocarcinoma • Non-small cell lung cancer	2015 2014 2014
Rituximab (Rituxan, Mabthera)	CD20	• Non-Hodgkin's lymphoma • Chronic lymphocytic leukemia • Rheumatoid arthritis • Granulomatosis with polyangiitis	1997 2010 2006 2011
Siltuximab (Sylvant)	IL-6	• MulticentricCastleman's disease	2014
Tocilizumab (Actemra)	IL-6R	• Rheumatoid arthritis • Juvenile idiopathic arthritis	2010 2011
Trastuzumab (Herceptin)	HER2 (ERBB2/neu)	• Breast cancer (HER2+) • Gastric cancer (HER2+)	2006 2010

Effort has also been made to include agents that hold promise in major clinical trials.

Monoclonal Antibodies

This year marks the 30th anniversary of the Food and Drug Administration approval of the first mAb for human use.Few of the surface antigens present on the malignant cells and not on the surrounding normal cells are the excellent target for the specific antibodies to act. These tumor associated antigens are the ideal targets. The fragment antigen binding (Fab) of a monoclonal antibody, which recognizes and binds to antigens, is responsible for the highly specific targeting that is possible with such therapies.

The mAbs exert their anti-neoplastic effects through a multiplicity of mechanisms: by engaging host immune functions to attack the target cell; or by binding either to receptors or ligands, thereby blocking crucial cancer cell processes. Other mechanism includes a lethal payload carrier, such as a radioisotope or toxin, to the target cell (i.e., conjugated mAbs). Because their protein structure is digested by gastrointestinal fluids, mAbs are administered intravenously. In addition, they are not subject to significant drug interactions because they do not undergo hepatic metabolism [(4)].

Table 2

DRUG	TARGET	POSSIBLE INDICATION	TRIAL
3F8	GD2	Detection and treatment of neuroblastoma	Phase 2 Clinical Trials
Abagovomab	Act as surrogate antigen	Ovarian cancer	Phase 2 Clinical Trials
Adecatumumab (MT201)	EpCAM-CD326	Tumor cells (prostate, breast cancers)	Phase 2 Clinical Trials
Anatumomab mafenatox	Glycoprotein 5T4	Non-small cell lung cancer	Phase 2 Clinical Trials
Apolizumab (HulDIO, REMITOGEN™ SMART™)	HLA-DR β	Non-Hodgkin lymphoma, Chronic lymphocytic leukemia	Phase 2 Clinical Trials
Bavituximab	Phosphatidylserine	Cancer, viral infections	Phase 2 Clinical Trials
Bivatuzumab mertansine	CD44 v6	Squamous cell carcinoma	Phase 2 Clinical Trials
Cantuzumab mertansine (huC242-DMl, SB408075)	Mucin CanAg	Colorectal tumor, Pancreatic cancers	Phase 2 Clinical Trials
Citatuzumab bogatox VB6-845	TACSTD1	Ovarian cancer, solid tumors	Pre clinical trials
Cixutumumab	IGF-1 receptor	Solid tumors	Phase 1 Clinical Trials
Clivatuzumabtetraxetan yttrium (Y-90)	MUC1	Pancreatic cancer	Phase 2 Clinical Trials
Conatumumab (AMG-655)	TNFRSF10B, TRAIL-R2 (CD262)	Solid tumors	Clinical trials
Dacetuzumab (SGN 40)	CD40	Non- Hodgkin's lymphoma and hematological malignancies	Clinical trials
Daratumumab	CD38	Multiple myeloma	Clinical trials
Ecromeximab (KW2871)	GD3 ganglioside	melanoma	Phase II trials
Elsilimomab (B-E8)	IL-6	Lymphoma/Myeloma	Pre clinical trials
Ertumaxomab (Rexomun®)	HER2/neu, CD3	Breast cancer	Phase 2 Clinical Trials
Etaratuzumab MEDI-522 (Abegrin® or Vitaxin)	Integrin αv β3	Several type of cancers	Pre clinical trials
Farletuzumab (MORAb-003)	FR-α	Ovarian cancer	Phase 3 trials
Figitumumab (CP-751871)	IGF-1 receptor	Various types of cancers	Phase 2 clinical trials
Galiximab (IDEC-114)	CD80	B cell lymphoma, Non-Hodgkin's lymphoma, Psoriasis	Phase 2 clinical trials
Girentuximab (Rencarex®cG250, WX-G250)	Carbonic anhydrase 9 (CA-LX, MN, G250)	Renal cell carcinoma	Phase 2 clinical trials
Glembatumumab vedotin(CR011,CDX-011)	GPNMB (transmembrane glycoprotein NMB)	Cancer cells expressing NMB: melanoma, breast cancer	Phase 2 clinical trials
Inotuzumab ozogamicin (CMC-544)	CD22	Diffuse large B cell lymphoma, Non-Hodgkin lymphoma	Phase 2 clinical trials
Iratumumab (MDX-060)	CD30	CD30-positive lymphoma including Hodgkin's disease	Phase 2 clinical trials
Labetuzumab (hMN14, CEACIDE™)	CEA	Colorectal tumor	Phase 2 clinical trials
Lexatumumab (ETR2-ST01)	TRAIL-R2 (AP02)	Tumors	Preclinical trials
Lintuzumab	CD33	AML	Preclinical trials
Lucatumumab	CD40	Cancer like multiple myeloma, non-Hodgkin's or Hodgkin's lymphoma	Phase 2 clinical trials
Lumiliximab (IDEC-152,P5E8)	CD23	Chronic lymphocytic leukaemia, Allergic asthma	Phase 2 clinical trials
Mapatumumab	TRAIL-receptor (death receptor 4)	Several tumors	Preclinical trials
Mitumomab (BEC2)	GD3 ganglioside	Melanoma and Small cell lung carcinoma	Phase 3 clinical trials
Naptumomab estafenatox (ABR-217620, ANYARA, TTS CD3)	TPBG (trophoblast glycoprotein, 5T4)	Several tumors	Phase 2 clinical trials
Necitumumab (IMC-11F8)	EGFR	Several tumors	Phase 2 clinical trials
Olaratumab (IMC-3G3)	PDGF-Rα	Solid tumors	Phase 1 clinical trials
Oportuzumab monatox. (PROXINIUM™ VICINIUM™	EpCAM, and others	Several tumors	Phase 3 clinical trials
Oregovomab (OVAREX®)	MUC16, CA-125	Ovarian tumors	Phase 2 clinical trials
Pritumumab	Vimentin	Brain cancer	Phase 2 clinical trials
Robatumumab (SCH 717454)	CD221	Colon sarcoma, Blood cancers	Phase 2 clinical trials
Tigatuzumab (CS-1008)	TRAIL-R2 OrDR5	Several tumors (colorectal, pancreas, ovary)	Phase 2 clinical trials
Ticilimumab (CP-675,206)	CD 152 (CTLA-4)	Melanoma/small cell lung cancer/prostate cancer	Phase 3 clinical trials
Veltuzumab	CD20	Non-Hodgkin's lymphoma	Phase 2 clinical trials
Volociximab	Integrin α5β1	Solid tumors	Phase 2 clinical trials
Zalutumumab (HuMax-EGFR)	EGFR	Squamous cell carcinoma resistant to chemotherapy	Phase 3 clinical trials

Several monoclonal antibodies have been approved for the treatment of neoplastic diseases.(Table-1)

A number of monoclonal antibodies are in the clinical trials which may supplement our armamentarium against cancer. A short list of these agents under trial is as follows-(Table-2)

Signal Pathway Inhibitors / Small Molecules

The normal cell growth and replication is a very complicated and organised process. DNA contains the code which is transcripted into m-RNA and this is further translated into proteins, including growth factors that bind to receptors of the same cell or surrounding or distant cell. This binding activates signalling pathways that relay information back to the nucleus, activates mechanisms responsible for cell division and proliferation. The main difference between malignant and normal cells is that malignant cells can proliferate indefinitely and have lost the normal signals that are responsible for apoptosis.

These abnormalities are targeted by these agents to inhibit cell proliferation, induce apoptosis or both. However, the basic flaw that undermines this approach is that very few malignancies are due to a single abnormality and most cancer cells sustain several mutations before turning malignant. This makes most malignancies in individual unique in nature, and thereby one approach doesn't fit all.

Generally, signal pathway inhibitors were administered orally because they are not degraded in the gastrointestinal tract. Furthermore, they are manufactured by chemical. Process that is less expensive than the bioengineering required for monoclonal Antibodies. They achieve less specific targeting than do monoclonal antibodies, as is evident in the multitargeting nature of the kinase inhibitors such asimatinib, dasatinib, sorafenib, and sunitinib. Unlike monoclonal Antibodies, most signal pathway inhibitors are metabolized by cytochrome P450 enzymes (CYP450), which could result in interactions with the potent inhibitors of CYP450 such as warfarin, macrolide antibiotics, azole antifungals, certain anticonvulsants, protease inhibitors, etc. Whereas monoclonal Antibodies have half-lives ranging from days to weeks (and are therefore usually administered once every one to four weeks), most signal pathway inhibitors have short half-lives (few hours) and require daily dosing [(4)].

These agents can be broadly classified into

Protein Tyrosine Kinase Inhibitors (TKIs)- Protein Tyrosine Kinases are transmembrane or cytosolic enzymes that bind to its receptors leading to activation of downstream signalling pathways. These include growth factors, differentiation factors & hormones. More than 100 protein tyrosine kinases have been identified, including.

a. Epidermal Growth Factor Receptor (EGFR/Erb B/HER 1-4)
b. Platelet Derived Growth Factor Receptor (PDGFR)
c. Vascular Endothelial Growth Factor Receptor (VEGFR)
d. Cytosolic Abelson (Abl) Tyrosine Kinase
e. Other include JAK2/mTOR/MEK/ALK/BTK/KIT/PI3K/RET etc.

Proteasome Inhibitors- Proteasome is a multi-enzyme complex that is responsible for the degradation of proteins that regulate cell cycle progression.

Blocking Intracellular Pathways- Downstream signalling pathways within the cancer cells can also be inhibited. Examples include Ras, Raf pathways etc.

Molecules Targeting Epigenome- Human gene expression patterns are controlled and coordinated by the activity of a diverse array of epigenetic regulators, including histone methyltransferases, acetyltransferases, and chromatin remodelers. Deregulation of these epigenetic pathways can lead to genome-wide changes in gene expression, with serious disease consequences. Currently the only epigenetically directed therapies in clinical practice are inhibitors of DNA methyltransferases and histone deacetylases (HDAC).

Poly(ADP-Ribose) (PARP) Inhibitors - Cancer cells may harbour defects in DNA repair pathways leading to genomic instability. This can foster tumorigenesis but also provide a weakness that can be exploited therapeutically. Tumors with compromised ability to repair double-strand DNA breaks by homologous recombination, including those with defects in the *BRCA1* and *BRCA2* genes, are highly sensitive to blockade of the repair of DNA single-strand breaks, via the inhibition of the enzyme poly(ADP-ribose) (PARP). This provides the basis for a *synthetic lethal* approach to cancer therapy, which is showing considerable promise in the clinic.

Miscellaneous Agents

Following is a comprehensive list of small molecules approved by USFDA for use in treatment in cancer. (Table-3)

Many of these agents are in various phases of clinical trials. Important of them are enlisted below-

Over the last few decades, the success of small molecule cancer drugs over conventional chemotherapy has been clearly demonstrated. The main focus of molecularly targeted therapy using small molecule inhibitors have been the pathways that are usually deregulated in cancer, thus inhibiting cancer cell survival and proliferation. Majority of the inhibitors that have been developed and currently in clinical use target the kinases, which include the receptor molecules as well as downstream regulators. With the exception of proteasome inhibitor bortezomib, small molecule inhibitors of MMPs and those targeting apoptosis have albeit been extensively studied, but are yet to be approved for clinical use. Identifying specific genes/proteins, and understanding the mechanism(s) underlying the progression of each cancer will help design novel strategies to further improve the efficacy of current drugs and possibly identification of novel agents. The advantages of using a combination of different agents that inhibit several pathways or use of small molecule inhibitors in combination with radiation therapy can also be explored. In this regard, combination therapies using small molecule drugs and monoclonal Antibodies have been exploited and are emerging to be a promising anti-cancer strategy.

The rate at which new drugs are discovered and developed is frustratingly slow, with an increasing failure rate of most drugs at the clinical level. It is therefore of utmost importance to address the limitations of these drugs so as to reduce the delay in approval of these drugs for clinical use.

Table 3

Drug	Target	Indication	Year of approval
Afatinib (Gilotrif)	EGFR (HER1/ERBB1), HER2 (ERBB2/neu)	o Non-small cell lung cancer (with EGFR exon 19 deletions or exon 21 substitution (L858R) mutations)	2013
		o Squamous cell cancer lung	2016
Aldesleukin (Proleukin)	IL-2	• Renal cell carcinoma	1998
		• Melanoma	
Alectinib (Alecensa)	ALK	o Non-small cell lung cancer (with ALK fusion)	2015
Axitinib (Inlyta)	KIT, PDGFRβ, VEGFR1/2/3	o Renal cell carcinoma	2011
Belinostat (Beleodaq)	HDAC	o Peripheral T-cell lymphoma	2014
Bortezomib (Velcade)	Proteasome	• Multiple myeloma	2008
		• Mantle cell lymphoma	2006
Bosutinib (Bosulif)	ABL	• Chronic myelogenous leukemia (Philadelphia chromosome positive)	2013
Cabozantinib (Cabometyx [tablet], Cometriq [capsule])	FLT3, KIT, MET, RET, VEGFR2	• Medullary thyroid cancer	2012
		• Renal cell carcinoma	2016
Carfilzomib (Kyprolis)	Proteasome	• Multiple myeloma	2015
Ceritinib (Zykadia)	ALK	• Non-small cell lung cancer (with ALK fusion)	2014
Cobimetinib (Cotellic)	MEK	• Melanoma (with BRAF V600E or V600K mutation)	2015
Crizotinib (Xalkori)	ALK, MET, ROS1	• Non-small cell lung cancer (with ALK fusion or ROS1 gene alteration)	2011
Dabrafenib (Tafinlar)	BRAF	• Melanoma (with BRAF V600 mutation)	2013
Dasatinib (Sprycel)	ABL	• Chronic myelogenous leukemia (Philadelphia chromosome positive)	2007
		• Acute lymphoblastic leukemia (Philadelphia chromosomepositive)	2006
Erlotinib (Tarceva)	EGFR (HER1/ERBB1)	• Non-small cell lung cancer (with EGFR exon 19 deletions or exon 21 substitution (L858R) mutations)	2004
		• Pancreatic cancer	2005
Everolimus (Afinitor)	mTOR	• Pancreatic origin neuroendocrine tumor	2011
		• Gastrointestinal, or lung origin neuroendocrine tumor	2016
		• Renal cell carcinoma	2009
		• Nonresectable subependymal giant cell astrocytoma associated with tuberous sclerosis	2012
		• Breast cancer (HR+, HER2-)	2012
Gefitinib (Iressa)	EGFR (HER1/ERBB1)	• Non-small cell lung cancer (with EGFR exon 19 deletions or exon 21 substitution (L858R) mutations	2015
Ibrutinib (Imbruvica)	BTK	• Mantle cell lymphoma	2013
		• Chronic lymphocytic leukemia	2014
		• Waldenstrom'smacroglobulinemia	2015
Idelalisib (Zydelig)	PI3Kδ	• Chronic lymphocytic leukemia	2014
		• Follicular B-cell non-Hodgkin lymphoma	2014
		• Small lymphocytic lymphoma	2014
Imatinib (Gleevec)	KIT, PDGFR, ABL	• GI stromal tumor (KIT+)	2012
		• Dermatofibrosarcoma protuberans	2016
		• Multiple hematologic malignancies including Philadelphia chromosome-positive ALL and CML	2001
Ixazomib (Ninlaro)	Proteasome	• Multiple Myeloma	2015
Lapatinib (Tykerb)	HER2 (ERBB2/neu), EGFR (HER1/ERBB1)	• Breast cancer (HER2+)	2013
Lenvatinib (Lenvima)	VEGFR2	• Renal cell carcinoma	2016
		• Thyroid cancer	2015
Nilotinib (Tasigna)	ABL	• Chronic myelogenous leukemia (Philadelphia chromosome positive	2013
Olaparib (Lynparza)	PARP	• Ovarian cancer (with BRCA mutation)	2014
Osimertinib (Tagrisso)	EGFR	• Non-small cell lung cancer (with EGFR T790M mutation)	2015
Palbociclib (Ibrance)	CDK4, CDK6	• Breast cancer (ER+, HER2-)	2016
Panobinostat (Farydak)	HDAC	• Multiple Myeloma	2015
Pazopanib (Votrient)	VEGFR, PDGFR, KIT	• Renal cell carcinoma	2009
		• Soft tissue sarcoma	2012
Ponatinib (Iclusig)	ABL, FGFR1-3, FLT3, VEGFR2	• Chronic myelogenous leukemia	2012
		• Acute lymphoblastic leukemia (Philadelphia chromosome positive)	2012
Regorafenib (Stivarga)	KIT, PDGFRβ, RAF, RET, VEGFR1/2/3	• Colorectal cancer	2012
		• Gastrointestinal stromal tumors	2013
Romidepsin (Istodax)	HDAC	• Cutaneous T-cell lymphoma	2009
		• Peripheral T-cell lymphoma	2011
Ruxolitinib (Jakafi)	JAK1/2	• Myelofibrosis	2011
		• Polycythemiavera	2014
Sonidegib (Odomzo)	Smoothened(SMO)	• Basal cell carcinoma	2015
Sorafenib (Nexavar)	VEGFR, PDGFR, KIT, RAF	• Hepatocellular carcinoma	2013
		• Renal cell carcinoma	2005
		• Thyroid carcinoma	2013
Temsirolimus (Torisel)	mTOR	• Renal cell carcinoma	2007
Tofacitinib (Xeljanz)	JAK3	• Rheumatoid arthritis	2012
Trametinib (Mekinist)	MEK	• Melanoma (with BRAF V600 mutation)	2014
Vandetanib (Caprelsa)	EGFR (HER1/ERBB1), RET, VEGFR2	• Medullary thyroid cancer	2011
Vemurafenib (Zelboraf)	BRAF	• Melanoma (with BRAF V600 mutation)	2011
Venetoclax (Venclexta)	BCL2	• Chronic lymphocytic leukemia (with 17p deletion)	2016
Vismodegib (Erivedge)	PTCH, Smoothened	• Basal cell carcinoma	2012
Vorinostat (Zolinza)	HDAC	• Cutaneous T-cell lymphoma	2006
Ziv-aflibercept (Zaltrap)	PIGF, VEGFA/B	• Colorectal cancer	2012

With more than 60% of cancer deaths occurring in low and middle income countries, newer approaches are urgently warranted to identify and develop cost effective drugs. Future studies on small molecule cancer drugs should also focus on alternative strategies so as to develop newer drugs targeting novel pathways while striving to improve the efficacy of currently marketed drugs.

Gene Therapy

Gene therapy implies any procedure intended to treat or alleviate a disease by genetically modifying the cell of a

patient either by blocking the expression of the oncogene or by replacing the missing or defective tumor suppressor gene[6]. The material to be transferred into patient cells may be genes, gene segments, or oligonucleotides. Gene therapy can be broadly broken down into three categories- immunotherapy, oncolytic virotherapy and gene transfer. It can be in vivo (intradermal injection of a metastatic nodule, or intra-vesical therapy for superficial bladder cancer) or ex vivo (transgene)[7].

Target cells may be normal cells, cancerous cells, immune mediated cells, or pluripotent stem cells. Once the transgene enters a cancer cell, it may assist in its death or restore normal cellular functions, whereas for normal cells, the transgene can protect them from drug-induced toxicities, or activate an immune cell to get rid of the cancer cell. Gene and vector-based molecular therapies for cancer comprise a wide range of treatment modalities to modify cancer cells, normal cells, and/or a tumor microenvironment [8].

The evolution from minority clone to lethal metastases follows branched evolution. Thus, tumors with high level of intratumor heterogeneity and genomic instability could be more likely to escape from targeted therapies such as gene therapy, unless such a branched evolution is taken into consideration. Hence, gene therapy is somewhat difficult to achieve, with limited success. Presently, most approaches are for monogenic gene therapy, tackling one or more critical gene defects. Selection of the appropriate mode of gene therapy is based on the assessment of the immune status, and determination of the molecular nature of a patient's disease. With the recent increases in knowledge of molecular biology of various medical disorders, a more advanced and comprehensive gene therapy approach will ultimately become available, with anticipated improved results [9].

Table 4 List of GeneTherapies Under Evolution

Predominant action	Examples	Commercially available*	Clinical trials, Phases II,III,IV **
Gene transfer			
Non-Viral	Electroporation, nanoparticles, hydrodynamics, cationic liposomes, transposon, synthetic viruses		18,1,0
Bacterial	Escherichia coli, Salmonella, Clostridium, Listeria, CEQ508		6,0,0
Viruses			
ssDNA viruses	Adeno-Associated: Parvovirus		
dsDNA viruses	Adenoviruses: Ad5-D24, CG870, Ad5-CD/TKrep, Recombinant H103, Gutless adenovirus, OBP-301	ONYX-015	11,3,0
dsDNA viruses	Herpetic viruses: Herpes simplex-1, TVEC		42,10,0
ssRNA viruses	Lentiviruses: HIV-1, HIV-2, Simian IV, Feline IV.		8,2,0
dsRNA viruses	Reoviruses		9,1,0
Immunomodulation			
Active immunotherapy			41,3,0
	Single Tumor cell surface antigen vaccine		
	Antigen-specific plasmid-based vaccine: PSA, HER/2, Modified CEA vaccine.		
	Tumor cells, irradiated as vaccine		
	Genetically modified tumor cell vaccine: Using Poxvirus, Vaccinia virus, Recombinant fowl pox virus, Combination (TRICOM) (Prostvac-VF vaccine).		
Passive immunotherapy			219,29,2
	Antibodies against:	Rituximab	
	CD20 Protein on lymphoma cells	Rituximab	
	HER/2 receptor protein in breast cancer	Trastuzumab	
	CD52 Protein on CLL	Alemtuzumab	
	CD20 Protein on lymphoma cells	Ibritumomab	
	CD20 Protein on lymphoma cells	Tositumomab	
	EGFR Receptor on squamous CA	Cetuximab	
	EGFR Receptor on colorectal CA	Panitumumab	
	CD20 Protein on CLL	Ofatumumab	
	CD30 Protein on Hodgkin lymphoma cells	Brentuximab	
	HER/2 receptor protein in breast cancer	Pertuzumab	
	HER/2 receptor protein in breast cancer	Ado-Trastuzumab	
	CD20 Protein on CLL	Obinutzumab	
Adoptive immunotherapy			15,1,0
	Autologous activated T- lymphocytes	Sipuleucel-T	
	Genetically modified activated T-lymphocytes		
	Chimeric antigen receptor integrated T-lymphocytes		
	Activated dendritic cells		
	Genetically modified dendritic cells		
Immune enhancement			11,1,0
	Antibodies blocking CTLA-4 Inhibitors for malignant melanoma.	Ipilimumab	
Microenvironment modification			
Impact on vasculature	Humanized monoclonal antibodies against VEGFR-A	Bevacizumab	
	Anti-angiogenic genes (against VEGFR-A): Endostatin, Angiostatin		22,4,0

*Commercially approved medications by FDA US as of July 1, 2014. ONYX-015 was previously approved by FDA China.
**Clinical trials: Number of active clinical trials on gene therapy for cancer (Phases-II, -III, and –IV) as of July 1, 2014 (www.clinicaltrials.gov).

Gene transfer is mediated by vectors (viral or bacterial), physical (gene gun, ultrasound, gene vaccination, electroporation) & chemical methods (cationic liposomes & synthetic viruses)[9].

Immunotherapy in cancer can be classified into four major categories[10]. Active immunotherapy includes strategies that directly sensitize the host immune system to tumor-specific antigens, exemplified as cancer vaccines. Passive immunotherapy utilizes humanized or chimeric antibodies to specifically target tumor antigens without direct activation of the immune system. Adaptive immuno-therapy utilizes patients' immune cells, whether T-cells or dendritic cells, stimulated or manipulated ex vivo, then in-fused back, to better react against tumor antigens. Immune enhancement therapy aims to augment co-stimulatory molecules or block inhibitory molecules. Immune-based therapy may include one or more of the above approaches, either as distinct immunotherapy treatment, or in combination with other modalities of cancer therapy. This can be achieved by-

1. Autologous stimulated T-lymphocytes
2. Autologous activated T-lymphocytese.g.sipuleucel - T
3. Genetically modified activated T-lymphocytes
4. Chimeric antigen receptor integrated into T-lymphocytes
5. Genetically modified dendritic cells
6. Genetically modified tumor cell vaccine
7. Single-antigen plasmid-based vaccine

Oncolytic viruses are therapeutically useful anticancer viruses that will selectively infect and damage cancerous tissues without causing harm to normal tissues.

Each virus has a specific cellular tropism that determines which tissues are preferentially infected, and hence, what disease is caused. Rabies virus, for example, damages neurons, hepatitis B virus damages hepatocytes, HIV damages helper T lymphocytes and influenza virus damages airway epithelium. Many, if not most, naturally occurring viruses have a preferential, although nonexclusive, tropism for tumors and tumor cells. This probably has more to do with tumor biology than with virus biology since most tumors have evolved not only to avoid immune detection or destruction, but also to resist apoptosis and translational suppression, which are the key responses used by normal cells to limit a virus infection. Oncolytic viruses can kill infected cancer cells in many different ways, ranging from direct virus-mediated cytotoxicity through a variety of cytotoxic immune effector mechanisms.

Gene Therapy Implementation

Once genetic materials are transferred into target cells and incorporated into nuclear genetic DNA, they may induce silencing, down-regulation, modification, or re-pair of the target cell genes. Depending on the intensity of the gene expression, it may lead to cell death and tumor necrosis (as with the suicide gene), or impaired cell growth with tumor regression (as with the silencing gene). Modification of the gene may improve the response from subsequent cancer therapy, such as chemotherapy, immunotherapy, or radiation. Repair of the target gene may help in preventing subsequent malignancy or cancer-related complications such as thrombosis. They may also be helpful in the future by preventing hereditary cancer syndromes.

CONCLUSION

Although there as been an explosion in the armamentarium against cancer as far as targeted therapy in concerned, we need to further intensify our efforts as the era of 'personalised medicine' dawns on us and the concept of quality of life becomes more relevant in a developing country like ours.

References

1. Berretta m, di francia r, tirelli u. Editorial – The new oncologic challenges in the 3rd millennium. *WCRJ* 2014; 1: e133.
2. De monaco a, faioli d, di paolo m, catapano o, d'orta a, del buono m, del buono r, di francia r.Pharmacogenomics markers for prediction response and toxicity in cancer therapy WCRJ 2014; 1: e276.
3. Carter p. Improving the efficacy of antibody-based can-cer therapies. *Nat Rev Cancer* 2001; 1: 118-129.
4. S Di Martino et al Overview of FDA approved anti-cancerdrugs used for targeted therapy;WCRJ 2015; 2(3):e 553
5. Deanna Cross, James K. Burmester, Gene Therapy for Cancer Treatment: Past, Present and Future, Clinical Medicine & Research, Volume 4, Number 3: 218-227
6. Strachan T, Read A: Gene therapy and other molecular genetic-based therapeutic approaches. In Human Molecular Genetics. 2nd edition. Edited by Strachan T, Read AP. New York: Wiley-Liss; 1999.
7. Miller AD: Retroviral vectors. *Curr Top Microbiol Immunol* 1992, 158:1-24.
8. Weichselbaum RR, Kufe D: Gene therapy of cancer. Lancet 1997, 349(Suppl 2):SII10-2
9. Magid H Amer, Gene therapy for cancer: present status and future perspective: *Amer Molecular and Cellular Therapies* 2014, 2:27
10. Reardon DA, Wucherpfennig KW, Freeman G, Wu CJ, Chiocca EA, Wen PY, Curry WT Jr, Mitchell DA, Fecci PE, Sampson JH, Dranoff G: An update on vaccine therapy and other immunotherapeutic approaches for glioblastoma. *Expert Rev Vaccines* 2013, 12(6):597-615.

How to cite this article:

Sahil Gupta *et al* (2017) 'Overview of Molecular Targeted Therapy in Cancer', *International Journal of Current Advanced Research*, 06(08), pp. 5502-5508. DOI: http://dx.doi.org/10.24327/ijcar.2017.5508.0739

****