Novel and emerging targeted-based cancer therapy agents and methods

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Abstract After several decades of uncovering the cancer features and following the improvement of therapeutic agents, however cancer remains as one of the major reasons of mortality. Chemotherapy is one of the main treatment options and has significantly improved the overall survival of cancer patients, but chemotherapeutic agents are highly toxic for normal cells. Therefore, there is a great unmet medical need to develop new therapeutic principles and agents. Targeted-based cancer therapy (TBCT) agents and methods have revolutionized the cancer treatment efficacy. Monoclonal antibodies (mAbs) and small molecule inhibitors (SMIs) are among the most effective agents of TBCT. These drugs have improved the prognosis and survival of cancer patients; however, the therapeutic resistance has subdued the effects. Several mechanisms lead to drug resistance such as mutations in the drug targets, activation of compensatory pathways, and intrinsic or acquired resistance of cancer stem cells. Therefore, new modalities, improving current generation of inhibitors and mAbs, and optimizing the combinational therapy regimens are necessary to decrease the current obstacles in front of TBCT. Moreover, the success of new TBCT agents such as mAbs, SMIs, and immunomodulatory agents has sparked further therapeutic modalities with novel targets to inhibit. Due to the lack of cumulative information describing different agents and methods of TBCT, this review focuses on the most important agents and methods of TBCT that are currently under investigation.

Introduction

Cancer is a complex invasive disorder and is one of the major reasons of a significant mortality rate worldwide. Cancer incidence is correlated with a combination of the interaction of oncogenes, tumor suppressor gene mutations, and environmental forces [1].

For several years, traditional chemotherapy has been the main treatment modality in cancer patients in addition to radiation therapy and surgery [2]. These agents and methods may lead to complete remission and be effective in reducing tumor size and metastasis. However, most chemotherapy agents kill dividing cancer and normal cells and have high incidence of life-threatening complications [2]. On the other hand, resistance to chemotherapy presented a major obstacle to attempt to increase the prognosis of patients. Tumor cell resistance (intrinsic and acquired) results from the genetic and epigenetic modifications occurring in cancer cells before or after chemotherapy.

Therefore, developing new therapeutic agents and methods that specifically kill tumor cells, spare normal cells, and overcome drug resistance is imminent.

Targeted-based cancer therapies (TBCTs) have significantly improved, and several specific agents and interesting approaches have been developed (Table 1) [3–8]. Moreover, the

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Table 1 Current methods in targeted-based cancer therapy (TBCT)

Agents and method	Subtypes (examples)
Inhibitors	Small molecule inhibitors of tyrosine kinases
	Intracellular signaling molecules
	Small molecule inhibitors of pro-survival molecules
	Inhibitors of RNA and DNA Inhibitors of PTM
	Inhibitors of EMT
Immunotherapy	Active (vaccination), passive (e.g., mAb therapy), CAR
Targeting hypoxia	PR-104A, TH-302, mitomycin C, tirapazamine, copper II complex
Induction of autophagy	Wortmannin, LY294002, bafilomycin A1, monensin
Induction of Tumor cell differentiation	Retinoic acid
Immunomodulatory (IMiD) agents	Ibrutinib, lenalidomide

EMT epithelial to mesenchymal transition, *CAR* chimeric antigen receptors

application of immunomodulatory (IMiD) agents has tremendously improved the survival of cancer patients.

Among several TBCT drugs, different types of inhibitors such as small molecule inhibitors (SMIs), monoclonal antibodies (mAbs), and antagonists have been described to control the progression of various cancers [5, 9, 10].

Targeting tumor cells using mAbs and SMIs against receptor tyrosine kinases (RTKs) or intracellular kinases has been described in several review articles [5, 9, 11]. This review describes the most important agents and methods of TBCT and the recent advances in the field of targeted cancer therapy.

Small molecule inhibitors

SMIs are chemical substances that interrupt with molecules required for cell growth and function. These agents specifically target molecules with a unique construction that differs from traditional chemotherapy drugs. SMIs are used for the treatment of various diseases such as autoimmune and malignant disorders [5, 12].

Currently, several inhibitors are in clinical use or are under investigation in pre-clinical and clinical stages. SMIs of tyrosine kinases (tyrosine kinase inhibitors (TKIs)) are one of the major groups.

Afatinib, erlotinib, lapatinib, ibrutinib, and sunitinib are examples among the current approved TKIs for cancer treatment. Moreover, new SMIs targeting RTKs such as AXL and ROR1 are promising drugs that are in pre-clinical settings [5, 9, 13].

Recently, several new and interesting inhibitors have emerged and will be discussed in following sections.

Inhibitors of pro-survival signaling pathways

Several inhibitors have been developed to target the intracellular key proteins, in which most of them are dysregulated pro-survival or signaling molecules. Upregulation of pro-survival modulators and suppression of anti-apoptotic proteins are important for tumor cell survival. Targeting these molecules such as Bcl family members involved in cell survival signaling pathways are of great importance.

Pro-survival inhibitors

Navitoclax (ABT-263) is a Bcl-2/Bcl-XL/Bcl-w inhibitor that binds to Bcl-2 family proteins with higher affinity than other Bcl-2 inhibitors (100–1000-fold greater). Bcl-XL is highly expressed on platelets, and navitoclax induced thrombocytopenia in treated patients [14]. Significant clinical benefit has been demonstrated in chronic lymphocytic leukemia (CLL) patients [15]. Navitoclax induced partial remission in one third of relapsed CLL patients. Pre-clinical and clinical studies have shown that navitoclax may enhance sensitivity of small cell lung cancer cells to standard cytotoxic agents [15, 16]. Moreover, combination of TKIs with pro-survival inhibitors, such as navitoclax, might also sensitize tumor cells to treatment [17]. Navitoclax is under investigation in combination with mAbs (e.g., rituximab), TKIs (e.g., erlotinib), and other drugs in clinical trials. Leukemic cells in the bone marrow (BM) are less responsive to navitoclax due to the contact with stromal cells and upregulation of anti-apoptotic proteins [18]. Therefore, combination of other agents that release leukemic cells from BM or lymph nodes might increase the efficiency of navitoclax. Combination of navitoclax and ibrutinib may be an appropriate strategy to target resident tumor cells in tissues. Treatment of CLL patients with ibrutinib increased the number of blood lymphocyte and resulted in lymphocytosis. A majority of these CLL cells are released from lymph nodes followed by rapid resolution of enlarged lymph nodes [19]. Released leukemic cells loss their contact with supporting stromal cells and become deprived of survival contacts [19].

PARP inhibitors as part of DNA repair machinery

Poly ADP ribose polymerases (PARP) have been known as an important DNA repair enzyme group. These enzymes are present in the nucleus and are activated by DNA damage. Due to the crucial role of PARP enzymes, PARP inhibitors are potential and novel therapeutic drugs for cancer treatment.

Several PARP inhibitors are under investigation as single agents or in combination with other DNA-damaging drugs

Table 2 Current inhibitors in clinical settings or approved for cancer treatment

Name	Trade name	Mol. mass (g/mol)	Target molecule/s	FDA approved or in phase III clinical trial for treatment
Anastrozole	Arimidex	293.366	Aromatase inhibitor	Breast cancer
Alitretinoin	Panretin	300.435	Retinoic acid receptors retinoid X receptors	Cutaneous lesions in patients with AIDS-related Kaposi sarcoma
Aflibercept	Zaltrap	96900	VEGF	Metastatic colorectal cancer
Belinostat	ND	318.348	HDACs	T cell lymphomas
Bexarotene	Targretin	348.478	Retinoic acid receptors	CTCL
Bortezomib	Velcade	384.237	Proteasome inhibitors	Multiple myeloma, MCL
Carfilzomib	Kyprolis	719.91	Proteasome inhibitors	Multiple myeloma
Deforolimus	ND	990.2	mTOR	Advanced soft tissue, bone sarcoma
Denileukin diftitox	Ontak	57647.3	IL-2 receptors	CTCL
Entinostat	ND	376.4	HDACs	Breast cancer, Hodgkin's lymphoma, lung cancer
Everolimus	Afinitor	958.224	mTOR	Advanced kidney cancer, subependymal giant cell astrocytoma, MBC, pancreatic neuroendocrine tumors, advanced renal cell carcinoma
Exemestane	Aromasin	296.403	Aromatase inhibitor	Breast cancer
Ibrutinib	Imbruvica	440.49	Btk (IMiD agent)	CLL, MCL, DLBCL
Iniparib	ND	292.03	PARP	Glioblastoma
Lasofoxifene	Fablyn	563.64	ER	ER-positive breast cancer
Lenalidomide	Revlimid	259.261	IMiD agent	Multiple myeloma, CLL, MCL
Letrozole	Femara	285.303	Aromatase inhibitor	Breast cancer
Mocetinostat	ND	396.44	HDACs	Follicular lymphoma, Hodgkin's lymphoma, AML
Olaparib	AZD-2281	435.08	PARP	Ovarian, breast, prostate cancers
Pladienolide	ND	536.7	spliceosome	Gastric cancer,
panobinostat	ND	349.426	HDACs	Hodgkin's lymphoma, CTCL
Pralatrexate	Folotyn	477.47	Antifolate	TCL
Raloxifene	Evista	473.584	ER	ER-positive breast cancer
Romidepsin	Istodax	540.695	HDACs	CTCL
Rucaparib	ND	323.36	PARP	Ovarian, breast, prostate cancers
Sirolimus	Rapamune	914.172	mTOR	Hepatocellular carcinoma
Tamoxifen	Nolvadex/Istubal/ Valodex	563.638	ER	ER-positive breast cancer
Temsirolimus	Torisel	1030.28	mTOR	Renal cell carcinoma
Toremifene	Fareston	405.959	ER	ER-positive breast cancer, prostate cancer
Tretinoin	Vesanoid	300.4412	Retinoic acid receptors	Acute promyelocytic leukemia
Veliparib	ND	244.29	PARP	Melanoma, breast cancer, NSCLC
Vorinostat	Zolinza	264.32	HDACs	CTCL

AIDS acquired immunodeficiency syndrome, *VEGFR* vascular endothelial growth factor receptor, *HDAC* histone deacetylase, *CTCL* cutaneous T cell lymphoma, *MCL* mantle cell lymphoma, *mTOR* mammalian target of rapamycin, *DLBCL* diffused large B cell lymphoma, *ND* not determined, *AML* acute myeloid leukemia, *TCL* T cell lymphoma, *ER* estrogen receptor, *PARP* poly ADP ribose polymerase, *NSCLC* non-small cell lung carcinoma

such as ionizing radiation. Currently, more than nine PARP inhibitors are in different stages of clinical settings for cancer treatment (Table 2).

PARP inhibitors are more proper for the treatment of patients with mutated *BRCA1/2* (breast cancer, early onset) genes associated with cancer than others. These mutations cause mistakes in DNA repair machinery and are lethal for cells when the DNA repair protein and PARP1 is inhibited [20].

Rucaparib (PF-01367338, AG-014699) is a PARP inhibitor, and pre-clinical studies have shown a better effect in combination with temozolomide [21]. In the first phase I trial, rucaparib combination with temozolomide was evaluated in 32 patients with different solid tumors [22]. Rucaparib combination with temozolomide showed PARP inhibition at all doses, and in a dose escalation evaluation, PARP inhibitory dose was determined to be 12 mg/m^2 with a constant dose of temozolomide at 100 mg/m^2/day. The maximal tolerated dose for the combination was 12 mg/m^2 for rucaparib and 200 mg/m^2/day for temozolomide. Mean of PARP inhibition at 5 h was determined to be 92 %, ranging from 46 to 97 %, and

DNA single-strand breaks were noted for all treated patients. No major side effect was observed for rucaparib alone, and no interaction with temozolomide was noted [22].

In a phase II study of the rucaparib, the combination with temozolomide in patients with metastatic melanoma was studied [23]. In this study, patients with no prior chemotherapy were evaluated. Treatment was given until disease progression. The response rate, median time to progression, and median overall survival were 17.4 %, 3.5, and 9.9 months, respectively. Myelosuppression was described in 54 % of patients [23].

Olaparib or AZD-2281 is an inhibitor of PARP1/2 with peak plasma concentration between 1 and 3 h and half-life of 5–7 h. In the first in-human phase I trial, the maximal tolerated dose was established as 400 mg/2 days [24]. Overall response rate and disease control rate were shown to be 47 and 63 %, respectively, in 19 ovarian breast or prostate patients with BRCA gene mutations [24]. In several clinical trials, olaparib has shown clinical benefits with anti-tumor activity in BRCA1- and BRCA2-deficient breast and ovarian cancer patients [24].

Veliparib (ABT-888), iniparib (BSI-201), CEP-9722, E7016 (GPI-21016), INO-1001, and LT-673 (BMN-673) are other potent PARP inhibitors that are under investigation in clinical trials as single agent or in combination therapy.

HDAC inhibitors

Normal cellular functions such as cell cycle arrest at different stages and apoptosis are mostly regulated by histone proteins that are modulated by protein acetylation [25]. Deregulation of histone acetylation has been shown to be related with aggressive disease and poorer response to the current treatments [26]. The acetylation states of proteins are modified by the opposing effects of histone acetyltransferases (HATs) and histone deacetylases (HDACs) [27].

HDACs are categorized into several classes based on homology to yeast HDACs and their dependence to zinc. These groups are class I (HDACs 1–3 and 8) (also named true HDACs), class II a/b (HDACs 4–7, 9, and 10), and class IV (HDAC 11) [25]. In contrast to HDAC class I members that are located in nucleus, class II HDACs are located in cytoplasm but can translocate into the nucleus. Class III HDACs [sirtuin enzymes (SIRTs 1–7)] are independent of zinc for function. Moreover, HDAC classes have different histone substrates. Histone is the main substrate of class I while both histone and nonhistone proteins are class II HDAC substrates, and conversely, nonhistone proteins act as class III HDAC substrates [25].

Moreover, based on the chemical structure, HDAC inhibitors are classified into several groups. These groups are hydroxamic acids (trichostatin A), carboxylic acids (valproate), aminobenzamides (entinostat), cyclic peptides (apicidin), epoxyketones (trapoxins), and hybrid molecules [28].

Protein acetylation and deacetylation are dysregulated in several tumors, including breast, ovarian, pancreatic cancers, multiple myeloma, T cell lymphoma (TCL), cutaneous T cell lymphoma (CTCL), melanoma, neuroendocrine tumors, leukemias, and Hodgkin's lymphoma [26]. HDAC inhibitors induce apoptosis, senescence, and differentiation and inhibit tumor cells angiogenesis and growth; however, they have no major effects on normal cells.

Clinical pieces of evidence demonstrated that HDAC inhibitors have promising anti-tumor effects. Vorinostat (Zolinza), panobinostat (LBH-589), belinostat (PXD-101), entinostat (MS-275 or SNDX-275), mocetinostat (MGCD0103), and romidepsin (Istodax) are promising HDAC inhibitors and target different members of HDACs [25].

Vorinostat and romidepsin have been approved by the FDA for the treatment of patients with refractory CTCL [28]. Vorinostat was the first HDAC inhibitor approved by the FDA for the treatment of progressive CTCL on October 6, 2006 (Table 2) [29]. Phase II clinical trials for evaluation of romidepsin were started in 1997 on various malignancies, and promising results were found in the treatment of CTCL and other peripheral T cell lymphomas. On November 5, 2009, the FDA approved romidepsin for the treatment of CTCL [30].

Currently, a new generation of HDAC inhibitors has been developed and some of them have entered the clinical trials, including CHR-3966, chidamide [31], AR-42, and hydroxamides quisinostat and abexinostat [28, 32]. Pre-clinical studies indicated that these inhibitors are more potent than the parental agents, with proper pharmacodynamic, pharmacokinetic, and lower side effects.

mTOR inhibitors

Mammalian target of rapamycin (mTOR), also recognized as FK506-binding protein 12-rapamycin-associated protein 1 (FRAP1), belongs to the phosphatidylinositide 3-kinase (PI3K) protein family. mTOR is an intracellular serine–threonine kinase that collects the growth and survival signals received by tumor cells as a central kinase. It is activated in tumor cells by different mechanisms such as RTK stimulation, oncogenes, and loss of tumor suppressor genes [33].

Different mTOR inhibitors such as deforolimus, everolimus, and temsirolimus have been approved for cancer treatment, and several other inhibitors are in pre-clinical and clinical stages (Table 2).

Deforolimus (ridaforolimus, AP23573, or MK-8669) is an analog of rapamycin. mTOR blocking by deforolimus induced a starvation effect in tumor cells by interfering with cell growth, cell division, metabolism, and angiogenesis [34]. Everolimus in combination with tamoxifen, letrozole, or exemestane has shown high clinical efficacy for the treatment of ER+ metastatic breast cancer patients [35]. This inhibitor was approved by the FDA for the treatment of advanced

recurrent colorectal carcinoma after failure of the treatment with sunitinib or sorafenib [36]. On August 29, 2012, the FDA granted accelerated approval for everolimus for the treatment of patients with tuberous sclerosis complex who have subependymal giant cell astrocytoma (SEGA). Everolimus is the first pediatric inhibitor drug to be approved by the FDA for the treatment of tumors that occur primarily during childhood [37].

Temsirolimus (Torisel) is a derivative of sirolimus and was approved by the FDA and the European Medicines Agency (EMA) in May and November 2007, respectively, for the treatment of patients with recurrent colorectal carcinoma [38]. It interferes with protein synthesis and controls tumor cell proliferation, growth, and survival. Temsirolimus has been shown to induce cell cycle arrest in the G1 phase and prevented tumor angiogenesis by inhibiting VEGF synthesis [39].

It has been shown that the PI3K/Akt/mTOR pathway is used by $ER^+/HER2^+$ tumors to escape control of anti-ER and HER2 therapies, including specific mAbs and SMIs. The combination of mTOR inhibitors with current ER/HER2-targeted therapies may be a promising approach for overcoming and preventing the development of drug resistance [40].

Targeting RNA translation in tumor cells

Several molecules involved in the process of RNA translation and protein synthesis are proper targets for special type of inhibitors that react with nucleic acids. RNA targeting is a developing approach to anti-tumor therapeutics that requires identification of specific inhibitors to target different RNA structures. Specific structures in RNA form several types of secondary structures like hairpin loops, internal loops, and bulged regions that are proper for the binding of inhibitors [6, 41].

Pre-messenger RNA (mRNA) splicing is an essential step in gene expression, and the maintenance of high fidelity of this process is vital to allow correct protein expression [42]. mRNA splicing is usually disrupted in cancer that might be due to altered expression of RNA-binding proteins, involved in mRNA splicing, and results in changes in normal process of alternatively spliced mRNAs [43]. Inhibitors or regulators that block or modify the splicing process of pre-mRNA might be proper for therapeutic applications. Currently, a few inhibitors are available with which to dissect the splicing process. Therefore, the identification of selective inhibitors that either prevent or change pre-mRNA splicing would be valuable for therapeutic applications [43].

Polyamines are polycationic amines that play important roles in sustaining cellular growth and activities. In cancer cells, their concentration is high and decrease in concentration

inhibits cellular growth and induces apoptosis [41]. Polyamines and analogues (e.g., 1-naphthylacetyl spermine (NASPM)) have been shown to interact and stabilize DNA and RNA. Some analogues have demonstrated strong activity against tumor growth in different types of cell lines [44]. Polyamine analogues do not substitute for the natural polyamines involved in normal cell function; therefore, they show selective anti-tumor activity [45]. Hence, polyamines are essential for cancer cell proliferation and targeting these agents is a proper strategy.

Moreover, several natural compounds and their synthetic derivatives were described to prevent splicing. GEX1A, FR901464, E7107, pladienolide B, pladienolide D, sudemycin, and spliceostatin A (SSA) are examples of these compounds that target the SF3b subunit of the U2 snRNP [43].

Madrasin is one of the mRNA splicing modulators that was reported by Pawellek et al. [43]. This inhibitor interfered with the early stages of spliceosome assembly and interrupts its assembly at the complex A. Madrasin is cytotoxic at high concentrations, while at low concentrations, it induces cell cycle arrest, stimulates reorganization of subnuclear protein localization, and controls splicing of several types of mRNAs [43].

Sudemycins (FR901464), an inhibitor of splicing, showed cytotoxic activity against tumor cells both in vivo and in vitro in xenograft models through targeting SF3b factor [46].

Pladienolide is a naturally occurring anti-tumor macrolide that inhibits the process of mRNA splicing. Pladienolide binds directly to spliceosome-associated protein 155 (SAP155, SF3b subunit 1), and the inhibitory activity is dose-dependent. Data suggested that SF3b factor is a potential anti-tumor drug target [47].

E7107 that targets the U2 small nuclear ribonucleoprotein (snRNP) subunit SF3b is a derivative of the pladienolide family. This product is in clinical trial, and promising results have been achieved [48, 49].

Other synthetic or natural inhibitors of mRNA splicing are under investigation in pre-clinical and clinical evaluation.

Targeting tumor cells by microRNAs

MicroRNAs (miRNAs or miR) are a type of noncoding small RNA molecules (21–25 nucleotides in length), which control gene expression. Several functions, including regulation of gene expression, tumor cell resistance to treatments, and behaving as tumor suppressor genes, have been described [50]. Dysregulation of miRNAs can be associated with several diseases and is involved in a variety of pathophysiologies due to aberrant expression [51, 52].

miRNAs are involved in tumor cell sensitivity to treatments. It has been shown that miR-7 sensitized non-small cell

lung cancer (NSCLC) cancer cells to paclitaxel [53]. Overexpression of miR-7 increased the sensitivity of NSCLC cells to paclitaxel by suppressing cell proliferation and induced cell apoptosis, while the inhibition of miR-7 disrupted the antiproliferative and pro-apoptotic effects of paclitaxel. miRNA such as miR-203 has been shown to downregulate TLR4 and the downstream cytokines in dendritic cells [51]. MiR-30e promoted apoptosis of acute myeloid leukemia (AML) cells to imatinib treatment through regulation of the oncogenic BCR-ABL protein. miRNA-105 has been demonstrated to inhibit cell proliferation and repressed PI3K/Akt signaling pathway in hepatocellular carcinoma [54].

Overexpression of miR-548 l inhibited NSCLC cell migration and invasion. MiR-548 l can bind to Akt1, and overexpression of Akt1 inverses the effects of miR-548 l in NSCLC cells. It is indicated that Akt1 is involved in the effects of miR-548 l and suppresses the migration and invasion of NSCLC cells [55].

Conversely, some miRNAs are involved in tumor cell resistance to different therapeutic agents. Overexpression of miR-1, miR-125a, miR-150, and miR-425 in glioblastoma increased the resistance of tumor cells to radiotherapy via upregulation of the cell cycle checkpoint response. Antagonists of these miRNAs sensitized glioblastoma cells to irradiation, suggesting their potential as targets for preventing therapeutic resistance [56].

Monoclonal antibodies: the most specific tools for targeted cancer therapy

Extracellular molecules such as cell surface receptors or soluble proteins are the conventional targets for mAbs. Several cluster of differentiation (CD) markers such as CD20, CD23, CD33, CD40, CD52, CD74, CD152 [cytotoxic T lymphocyte antigen-4 (CTLA-4)], CD279 [programmed death-1 (PD-1)], and CD274 [programmed death-ligand 1 (PD-L1)] are appropriate targets, which are under investigation for TBCT by mAbs (Table 3). MAbs against these molecules destroy tumor cells by different mechanisms such as complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated lysis (antibody-dependent cellular

Table 3 Current FDA-approved therapeutic monoclonal antibodies targeting non-tyrosine kinase molecules

Name	Trade name	Target	Antibody format	Targeted cancer (examples)
Alemtuzumab	Campath	CD52	Humanized IgG1	CLL, CTCL, TCL
Brentuximab vedotin (ADC)	Adcetris	CD30	Chimeric IgG1	Systemic anaplastic large cell lymphoma, Hodgkin's lymphoma
Catumaxomab	Removab	CD3 and EpCAM	Mouse bispecific mAb	Malignant ascites generated by an EpCAM-positive tumor malignant lung cancer
Dacetuzumab	–	CD40	Humanized IgG1	NHL
Denosumab	Prolia	RANKL	Humanized IgG2	Non-metastatic prostate cancer
Gemtuzumab ozogamicin	Mylotarg	CD33	Humanized IgG4	AML
Ibritumomab tiuxetan (ADC)	Zevalin	CD20	Mouse IgG1	B cell NHL
Ipilimumab (MDX-010/MDX-101)	Yervoy	CTLA-4	Humanized IgG1	Metastatic melanoma
Labetuzumab	CEA-CIDE	CEA	Humanized IgG1	Colorectal carcinoma
Lumiliximab	–	CD23	Humanized IgG1	CLL
Milatuzumab	–	CD74	Humanized IgG1	Multiple myeloma, NHL, CLL
Obinutuzumab	Gazyva	CD20	Humanized IgG1	CLL
Ofatumumab (HuMax-CD20)	Arzerra	CD20	Humanized IgG1	CLL
Pembrolizumab	Keytruda	PD-1	Humanized IgG4	Metastatic melanoma
Rituximab	Rituxan (MabThera)	CD20	Humanized IgG1	B cell NHL, CLL
Tositumomab	Bexxar	CD20	Mouse IgG2	B cell NHL, FL
Veltuzumab	–	CD20	Humanized IgG1	B cell NHL, CLL
Vivatuxin	–	Intracellular DNA-associated antigens	Radiolabeled chimeric IgG1κ	Malignant lung cancer
[90]Y-Ibritumomab tiuxetan	Zevalin	CD20	^{90}Y-labeled anti-, deliver Y-90, murine IgG1	Follicular B cell NHL

CLL chronic lymphocytic leukemia, *CTCL* cutaneous T cell lymphoma, *TCL* T cell lymphoma, *ADC* antibody–drug conjugate, *EpCAM* epithelial cell adhesion molecule, *NHL* non-Hodgkin's lymphoma, *AML* acute myeloid leukemia, *CTLA-4* cytotoxic T lymphocyte antigen-4, *CLL* chronic lymphocytic leukemia, *PD-1* programmed cell death 1 receptor, *FL* follicular lymphoma

cytotoxicity (ADCC)), and induction of direct apoptosis or necrosis [57–59]. MAbs targeting RTKs and several CD markers have been described in several articles and will not be discussed here; however, anti-CD20, anti-CD52, anti-CD152, anti-CD279, and anti-CD274 mAbs are described briefly as interesting tools for targeted cancer therapy.

Anti-CD20 mAb

CD20 is a signature B cell differentiation marker and is an activated-glycosylated phosphoprotein expressed on all B cells beginning at the pro-B stage (CD45R^{+}, CD117^{+}) with increased expression on mature B cells [60]. This antigen is expressed in several malignancies, including CLL, B cell lymphomas, hairy cell leukemia, Hodgkin's disease, melanoma cancer stem cells, myeloma, and thymoma [61].

Currently, there are two types of anti-CD20 mAbs that were approved for the treatment of B cell malignancies [62]. Rituximab (Rituxan) is a chimeric type I anti-CD20 mAb. This antibody is used as a single agent or combination therapy in relapsed or refractory indolent-non Hodgkin's lymphoma (NHL) [63] and CLL patients [64]. Rituximab exerts its cytotoxicity through CDC, ADCC, and weak direct apoptosis [65]. This antibody has become part of standard chemoimmunotherapy [(fludarabine, cyclophosphamide, and rituximab (FCR)] for most of untreated CLL patients [66].

Ofatumumab (Arzerra) was the second anti-CD20 mAb developed after rituximab for cancer treatment. It is a humanized type I anti-CD20 mAb targeting a different epitope on CD20 than the one targeted by rituximab and demonstrated higher activity in CDC and ADCC compared to rituximab, in vitro [62]. It was approved on October 20, 2011, for the treatment of CLL patients who are refractory to alemtuzumab and fludarabine treatment [65, 67, 68]. Recently (April 17, 2014), the FDA approved this mAb as single agent therapy for the treatment of CLL patients with no prior treatment or for those who are not eligible for chemotherapy (fludarabine-based therapy).

Obinutuzumab (Gazyva) is a novel, third-generation fully humanized anti-CD20 mAb (type II). The Fc region of obinutuzumab is glycol-engineered to result in higher affinity binding to the CD20 [69]. The mechanism of action of obinutuzumab is CDC and ADCC. Obinutuzumab showed an elevated ADCC as well as a markedly higher induction of direct cell death in vitro, compared to rituximab. This mAb is able to elicit actin-dependent, lysosomal cell necrosis in CLL cells in vitro. Obinutuzumab was approved by the FDA on November 1, 2013, for the treatment of CLL in combination with chemotherapy in previously untreated patients [70].

Currently, other anti-CD20 mAbs are in pre-clinical and clinical trial development.

Anti-CD52 mAb (alemtuzumab)

Alemtuzumab is a humanized anti-CD52 mAb for the treatment of B cell malignancies [71]. This mAb was approved on May 7, 2001, for the treatment of refractory CLL patients [72, 73].

The mechanism of action is mostly through ADCC and CDC [74, 75]. Alemtuzumab has serious side effects due to the widespread expression of CD52, including prolonged lymphopenia with an increased risk of infections [76]. About 20 % of CLL patients have been shown to have cytomegalovirus (CMV) reactivation usually occurring after 3–8 weeks of alemtuzumab treatment [77]. This antibody has also been tested with limited success in the treatment of NHL and for the preparation of patients with blood malignancies for BM transplantation. There are also clinical trials ongoing to test the ability of this antibody to prevent tissue rejection in transplantation [78, 79].

Anti-CTLA-4 and PD-1/PD-L1 mAbs

These molecules are involved in suppressing the immune system during different situations such as cancer. Targeting CTLA-4 and PD-1/PD-L1 antigens with mAbs has shown promising therapeutic results in several malignancies [80].

Several mAbs have been produced against these antigens, which are in preclinical and clinical settings for the treatment of various tumors; however, ipilimumab (anti-CTLA-4) and pembrolizumab (anti-PD-1) (Table 3) have been approved for the treatment of advanced melanoma on March 25, 2011, and September 4, 2014, respectively [80].

Ipilimumab is a fully human mAb that prevents CTLA-4 engagement and induces the activation of anti-tumor T cell immune responses. Targeting CTLA-4 is currently the main immunotherapeutic approach that has shown significant clinical benefit in melanoma patients [81].

Pembrolizumab is a blocking humanized mAb (IgG4) that binds to the PD-1 and inhibits its interaction with PD-L1 and PD-L2, leading to the activation of immune response.

Currently, these two mAbs are under clinical investigation for the treatment of several malignancies, including NSCLC, small cell lung cancer (SCLC), prostate, bladder, and metastatic hormone refractory cancers [82–84].

There are other approved mAbs which are used as the first- or second-line treatment for cancer, including CD74 (milatuzumab), CD40 (dacetuzumab), CEA (labetuzumab), and CD23 (lumiliximab) molecules (Table 3). Moreover, several other humanized mAbs are in various stages of clinical testing but not yet approved by the authorities to be used for therapy.

Targeting EMT in cancer

The epithelial to mesenchymal transition (EMT) is involved in many processes, including tissue and organogenesis as well as metastatic spread of cancer cells. Targeting this phenomenon by preventing the transition of EMT cells might be a proper strategy. EMT is classified into three types. Type 1 EMT is the process of embryogenesis during the embryo development, type 2 refers to the normal process of wound healing, and the process of cancer metastasis is classified as type 3. Loss of epithelial cell to cell junctions and apical–basal polarity are the major hallmarks of these three types [85].

Different intermediates such as transcription factors are responsible for EMT transition. The main regulators of EMT transition are transcription factors that are classified into three families, including zinc-finger E-box-binding (ZEB), TWIST, and SNAIL. SNAIL2, ZEB1, ZEB2, E47, KLF8, TWIST1, and FOXC2 transcription factors promote EMT in various cancer cells [86, 87].

The basic feature of EMT is the suppression of E-cadherin expression that is responsible for sustaining the cell junctions and cell–cell adhesion. SNAIL, TWIST, and ZEB expression can suppress E-cadherin and activate critical mesenchymal genes, including N-cadherin, vimentin, and fibronectin. These transcription factors regulate and activate the expression of mesenchymal genes while inhibiting epithelial gene expression [85].

Several mechanisms have been suggested to target EMT process for TBCT. These EMT targets are transcriptional regulators such as SNAIL, mediators (e.g., transforming growth factor beta (TGFβ)), noncoding RNAs, and cancer stem cells (CSCs). Moreover, targeting the tumor microenvironment interactions, the role in initiation, and termination of EMT might be considered [85].

Various inhibitors, including CX-4945, EW-7195, EW-7197, IN-1130, SB-431542, SD-208, SD-093, LY580276, LY-573636, and LY2152799, are among EMT inhibitors [88]. These drugs target ALK5 (or TGFβ type 1 receptor) kinase. Ligation of TGFβ receptors (types 1 and 2) by TGFβ will ultimately activate Smad proteins and their translocation to the nucleus. In the nucleus, Smad proteins regulate the expression of target genes including those involved in EMT; therefore, blocking ALK5 by these inhibitors has demonstrated promises in inhibiting EMT [89].

Immunomodulatory agents and targeted therapy

It has been shown that several types of chemotherapy agents have side effects on immune cells. Therefore, a special class of therapeutic agents called immunomodulatory (IMiD) agents was developed to be used in combination with chemotherapy or other targeted therapies to prevent immune system suppression. Later on, several groups showed that some of these drugs not only have IMiD effects, but also can directly kill tumor cells.

Currently, a few IMiD agents have been approved by the FDA for the treatment of B cell malignancies and several others are in pre-clinical or clinical settings. Lenalidomide and ibrutinib belong to this group [90].

Lenalidomide

Lenalidomide or Revlimid is a derivative of thalidomide and has several mechanisms of action. The anti-tumor and IMiD effects are mediated through regulating innate and specific immune responses. For instance, it changed the immunological profile of the tumor cell microenvironment by preventing the secretion of pro-survival cytokines such as TNFα, IL-1β, and IL-6, while favoring that of IL-2, IL-10, IL-12, and interferon γ (IFNγ) [91]. Moreover, it activated T and NK cells; inhibited tumor angiogenesis [92–94]; changed the balance of Th1/Th2 cell toward Th1; increased the expression of CD80, CD86, and HLA-DR; and stimulated the cytotoxic effects of T lymphocytes and natural killer cells [95].

Lenalidomide is mostly administrated for the treatment of patients with relapsed or refractory CLL [96, 97], multiple myeloma [98], MCL [99], and a few other lymphomas [91, 100]. The mechanism of action of lenalidomide exerts direct cell cycle arresting and pro-apoptotic effects on cancer cells, interrupts with physical and functional communication with the tumor microenvironment, and mediates immunostimulatory activity. The cell cycle arrest and the consequent anti-tumor effects of lenalidomide are through the upregulation of cyclin-dependent kinase inhibitors (CDKNs) [101].

Lenalidomide inhibited the immunosuppressive effects of myeloid-derived suppressor cells (MDSCs) and regulatory T cells by preventing the expression of the transcription factor forkhead box P3 (FOXP3). Indeed, this IMiD has shown robust anti-neoplastic effects in multiple myeloma patients previously subjected to stem cell transplantation while stimulating a transient increase in CD4$^+$ FOXP3$^+$ Tregs [102].

Ibrutinib

Ibrutinib (Imbruvica) is an inhibitor of Bruton's tyrosine kinase (Btk) that was reported in 2007 [103]. This inhibitor was developed from the PCI-29732 inhibitor [103]. It binds covalently with cysteine (Cys) 481 in the ATP-binding pocket of Btk.

Ibrutinib binds to the nonphosphorylated Btk and stabilizes this inactive conformation by internalizing Tyr 551 and prevents its phosphorylation. Ibrutinib inhibits other kinases, including Blk, Bmx, EGFR, Itk, and JAK3 [104]. These kinases have a cysteine residue in the homologous location to Btk.

Ibrutinib has shown to be 1000-fold more selective for inhibition of BCR signaling in B cells over TCR signaling in T cells [104, 105].

Currently, several trials are assessing ibrutinib in malignant disorders, including CLL, DLBCL, and Waldenström's macroglobulinemia, alone or in combination with other drugs [106].

Recent studies have showed that ibrutinib blocked IL-2-inducible tyrosine kinase (Itk) in T cells. Th1 cells, however, express another kinase called resting lymphocyte kinase (Rlk or Txk). Following ibrutinib treatment, Itk in Th cells is inhibited and only Th1 cells survived due to the activation of Rlk survival pathway [107]. This event changes the balance of Th1/Th2 toward Th1 cells that are the main cells activating immune cells against tumor cells and intracellular pathogens and prevents the production of autoreactive antibodies [107].

Targeting post-translational modification of proteins

Post-translational modification (PTM) of proteins by glycosylation, phosphorylation, acetylation, ubiquitination, and other modifications is essential in moderating protein function. Aberrant PTMs underlie a majority of human diseases, including cancer, and now, it is well established that altered modifications vary significantly for cancer cells compared to normal counterparts and each type of tumor might have a unique PTM signature [108]. Current development of analytical techniques and instrumentation, especially in mass spectrometry, has made it possible to recognize the type of protein PTMs in normal and cancer cells [109]. However, there are several issues that have not been solved such as determining the exact PMTs in tumor cells, mainly due to the intraclonal diversity of tumor cells within a population.

Generation of mAbs that target PTMs might be of high interest. However, due to the low immunogenicity of non-protein molecules, production of effective mAbs against the above-mentioned molecules is a major challenge. Moreover, for production of therapeutic mAbs, more information regarding PTMs in the protein of interest might be necessary.

It has been shown that IgM anti-ganglioside antibodies induced by melanoma cell vaccine correlated with survival of melanoma patients [110, 111]. Numerous anti-disialoganglioside mAbs have also been developed for clinical use and have been trialed in metastatic melanoma. Disialoganglioside GD2 is overexpressed on the surface of tumors of neuroectodermal origin and is an interesting target for mAbs [112].

Targeting PTMs is in early stages, and moreover, it is a challenging field and further investigations are warranted.

Inhibition of autophagy

Autophagy process was first described by Porter KR et al. [113]. Autophagy is a catabolic activity involving the degradation of cell components through the lysosomal machinery. Several enzymes, including 30 autophagy-associated molecules (Atg) and 50 hydrolases within the lysosomes, are involved in autophagy [114]. Cells use autophagy for the maintenance of cellular metabolism under starvation condition and to remove injured organelles under stress. This process is essential for normal growth control and is defective in several tumors as indicated as a pro-survival process in progressive tumor cells, leading to cancer resistance [115, 116].

Several pre-clinical and clinical trials are ongoing to develop therapeutic drugs to inhibit autophagy. Different inhibitors of autophagy are classified as early- or late-stage inhibitors. Inhibitors such as 3-methyladenine (3-MA), wortmannin, and LY294002 target the Vps34 (class III PI3K) and have been categorized as early-stage, and chloroquine (CQ), HCQ, bafilomycin A1, and monensin that prevent the lysosomal function are classified as late-stage inhibitors [117]. Microtubule-disrupting drugs like taxanes, nocodazole, colchicine, and vinca are defined as a separate class of autophagy inhibitors. CQ, HCQ, and quinacrine are being tested in clinical trials as promising anti-autophagy inhibitors.

Moreover, it is known that autophagy process happens in minor population of tumor cells and these inhibitors may have better effects in combination with other anti-cancer agents. Indeed, most clinical trials have used HCQ in combination with other inhibitors. Autophagy inhibition can also improve the anti-tumor immune responses. Immunotherapeutic methods such as dendritic cell (DC) vaccines, adoptive transfer of T cells, and administration of mAbs or cytokines are effective after the inhibition of the autophagic process [118].

Targeting the hypoxia induction

Hypoxia is a main feature of solid tumors, inducing an aggressive phenotype of tumors that is more resistant to therapies [119]. This process activates several pathways, including the hypoxia inducible factor (HIF), which mediates the effects of hypoxia in tumor tissues. Therefore, targeting the hypoxia by different inhibitors might be a proper treatment strategy [120].

HIF-1 inhibitors have been shown to decrease tumor cell proliferation, increase necrosis and apoptosis of the cells, and reduce tumor cell resistance to conventional therapies [121].

As HIF-1 is part of a transcriptional complex, special strategies are necessary to target hypoxia by inhibiting the HIF-1. Antisense strategies have been shown to decrease the expression of HIF-1a [122], and using a dominant-negative HIF-1a has been shown to decrease tumorigenicity of cancer cells by inhibiting glucose metabolism [123, 124].

Targeting protein–protein interactions by inhibiting HIF-1a is another approach to block the activity of HIF-1 [125]. For example, HIF-1a requires the transcriptional coactivator p300/CBP. Chetomin is an inhibitor of HIF-1 that prevented its binding to p300. It has been shown that chetomin disrupted the structure of the CH1 domain of p300 and inhibited its interaction with HIF. Moreover, systemic administration of chetomin blocked hypoxia-inducible transcription within tumors and inhibited tumor cell growth [126].

EZN-2968 is an antisense (16 nucleotide residues) of HIF-1a mRNA and reduces HIF-1a protein synthesis. In vitro studies showed that EZN-2968 inhibited tumor cell growth and downregulated HIF-1a-regulated genes. Furthermore, in vivo studies demonstrated decreased expression of HIF-1a mRNA in the livers of mice and anti-tumor activity in xenograft models of human prostate cancer [127]. EZN-2968 is under evaluation in patients with advanced solid tumors, and potential effects were observed in metastatic renal cell carcinoma and hepatocellular carcinoma [128]. Several other agents such as echinomycin (DNA intercalator) are under investigation in pre-clinical and clinical trials.

Hypoxic media might be used against tumor cells using prodrugs that will be activated in these situations. Tumor cell death has been known to increase by the use of bioreductive prodrugs from several years ago [129, 130]. These prodrugs are activated under reductive conditions that are found within the tumor hypoxic environments. In most situations, they interfere with DNA replication and lead to cell death [35]. The ability for these prodrugs to increase the killing effects of both irradiation and chemotherapy makes them potential agents in the treatment of solid tumors [131]. Several prodrugs have shown promising results in combination with radiotherapy [132].

Inducible nitric oxide synthase (iNOS) enzyme catalyzes and activates prodrugs under hypoxic situations and produces nitric oxide (NO). NO is also synthesized by other NO synthase enzyme [132]. NO that is released by donor drugs increases radio-sensitivity of human tumor cells in hypoxic conditions in vitro and mimics the effect of O_2 by fixation of radiation-induced DNA damage. Several studies have shown that NO has high an anti-tumor activity in high concentrations. Therefore, these prodrugs can overcome radio-resistant tumors [133]. Some of these prodrugs will be activated in the hypoxic microenvironment of the tumors (bioreductive produgs) [132].

Inducing tumor cell differentiation

Differentiated cells have low or no proliferative and metastasis activities. The approach of differentiation therapy of cancer has been introduced many years ago. Several encouraging in vitro and in vivo results have been obtained; however, the only successful clinical application has been all-transretinoic acid (ATRA)-based therapy of acute promyelocytic leukemia (APL) [134]. Pathogenesis of APL is related with a chromosomal translocation that disrupted retinoic acid receptor alpha (RARα) gene located on the short arm of chromosome 17 (q21) and resulted in an arrest of the early stage of promyelocyte differentiation. ATRA induces differentiation of APL blast cells [134].

This approach is useful for targeting CSCs by using compounds that induce the differentiation of these cells and therefore make them sensitive to other therapies. The main characteristic of CSCs is self-renewing and the capacity to differentiate to several cell populations. By inducing CSC differentiation, cells will become more susceptible to anti-tumor therapy and lose their ability to rebuild the tumor later. As described 37 years ago, retinoic acid (RA) is an appropriate molecule that induces cellular differentiation in embryonal carcinoma cell lines [135] through the upregulation of genes that promotes differentiation, like α-fetoprotein [136, 137] and downregulation of pluripotency-associated ones like Oct4 or telomerase [138].

RA induces cell cycle arrest at the G1 stage through the downregulation of cyclin D1 by promoting protein degradation and suppressing mRNA synthesis as well as reduction of the phosphorylation of retinoblastoma (Rb) protein [139]. RA has been demonstrated to induce cellular differentiation of keratinocytes, teratocarcinoma cells and APL, melanoma, and neuroblastoma cells in vitro [140–142]. Clinical studies have demonstrated some success, by combination of RA with other treatment protocols to overcome retinoid resistance [143]. In vitro studies have shown that combination of RA with HDAC inhibitors restores the expression of RARβ2 by renal cancer cells in xenografts, followed by inhibition of tumor growth [144] as well as in breast and thyroid cancers [145, 146]. Combination of RA and HDAC inhibitors has therapeutic effects in leukemia patients [147].

Conclusions

Current data have demonstrated the high efficiency of TBCT agents and methods. Even the data are encouraging, however, resistance to new agents, the plasticity of cancer cells, mutations, cross talks between intracellular survival pathways and with the microenvironment, upregulation of other oncogenes, the tumor heterogeneity, and CSC resistance are of the most important obstacles in front of researchers. Therefore, new applications such as appropriate drug combinations, new generation of mAbs, and different methods of TBCT may be necessary. Moreover, specific targeting of cancer stem cells might be important to prevent tumor cell resistance to current TBCT methods; however, more investigation on CSC phenotype, function, and homing places for each cancer type is

necessary. The early identification of mechanisms of tumor cell resistance is also important to change the treatment strategies or combine it with other methods. Finally, a better understanding of molecular, genetic, and epigenetic factors involving in the pathogenesis of cancer is warranted.

Conflicts of interest None

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