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Targeted Therapies in Hematological Malignancies

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1. Introduction

Tumorigenesis has a complex pathogenesis; with multiple genetic, proliferative, apoptotic and differentiation pathways aiding in development and growth of a tumor. Conventional chemotherapy has been the backbone for cancer treatment. The chemotherapeutic agents act on different phases of cell cycle of rapidly proliferating cells. Subsequently, in addition to effect of cancerous cells they also affect rapidly multiplying gastrointestinal lining cells, bone marrow and hair follicles leading to mucositis, diarrhea, various degrees of myelosuppression and alopecia. The search for less toxic agents has been ongoing for decades. Targeted therapy refers to directing a drug to a target that is either specific to or over expressed on the malignant cell. The concept of targeted therapy dates back to Paul Ehrlich who used the term "magic bullets" to describe a therapeutic agent which killed the microorganism but left the patient unharmed. Today the concept of targeted therapy is the most rapidly evolving field in drug discovery and cancer treatment.

One of the major hallmarks of successful targeted treatment is use all trans-retinoic acid (ATRA) for acute promyelocytic leukemia (APL). APL is distinguished by translocation between chromosome 15 and 17 (PML-RAR-α) which halts the differentiation at promyelocyte stage. ATRA induces the differentiation of promyelocytes into mature myeloid cells. Use of ATRA has improved response rate and survival rate in APL which was previously associated with a significantly worse outcome. In this chapter we review other major targeted agents. Due to limited space we emphasized primarily on chronic myeloid leukemia, multiple myeloma and lymphoma.

2. Chronic myeloid leukemia

Chronic myeloid leukemia (CML) is other example for successful targeted therapy treatment. The initial description of chromosome abnormality was first described by Nowell and Hungerford in two patients who were noted to have a loss of the long arm of chromosome 21 or 22 (later confirmed to be chromosome 22 and designated Philadelphia chromosome (Ph))(Nowell and Hungerford 1960; Nowell and Hungerford 1961). Subsequently, Rowley discovered that there is a reciprocal translocation between chromosome 9 and 22 in these patients(Rowley 1973). As a result of the translocation, cellular oncogene ABL on chromosome 9 and a segment of chromosome 22, the breakpoint cluster region BCR, fuse and cause activation of tyrosine kinase which is capable of inducing

the disease in mice. This established the fusion protein as the cause of malignant transformation in this disease. This led to the development of small molecule inhibitors of the mutant kinase and led to the discovery of Imatinib mesylate (Gleevec; Novartis, Basel, Switzerland).

Imatinib was the first tyrosine kinase inhibitor (TKI) to be developed and approved for CML in 2002. It was developed on the concept of designing synthetic compounds with chemical structures that are able to compete with the binding site in the kinase domain. Imatinib has demonstrated higher response rates (RR) and better tolerability compared to interferon and low dose cytarabine (Internation Randomised Study of Interferon and ST1571 (IRIS) trial) (Santos and Quintas-Cardama 2011). Recent update of IRIS trial reported that at 8 years follow up 83% had complete cytogentic response (cCR) and overall survival (OS) was 85% among patients with newly diagnosed, untreated CML in chronic phase (American Society of Hematology, 2009, Abstract 1126). Authors did report that 45% of patients in Imatinib arm discontinued treatment and one of the major reasons was development of resistance (Deininger M et al 2009). Over expression of the BCR-ABL1 oncogene, mutations in BCR-ABL1 that obstruct imatinib binding, alternative signaling pathways which reduce levels of transporters responsible for imatinib uptake have been associated with resistance. Second generation TKI approved in for patients with imatinib-resistant CML or imatinib intolerant are dasatinib (Sprycel; Bristol-Myers Suibb) and nilotinib (Tasigna; Novartis) and are highly active against most BCR-ABL1 mutations. Moreover, recently results of two phase III randomized trials comparing them to imatinib as first-line treatment showed higher major cytogenetic response (MCyR), major molecular response (MMR) and reduced rates of transformation to accelerated phase (AP) or blast phase (BP)(Kantarjian, Giles et al. 2007; Hochhaus, Baccarani et al. 2008). As a result, U.S. Food and Drug Administration (FDA) approved both dasatinib and nilotinib as first line therapies for patients with CML in chronic phase (CP).

There are patients who continue to experience poor outcomes despite the development of second generation TKIs. T315I mutation is the one of major cause of this resistance. Furthermore, none of the first and second generation TKIs eliminate leukemic stem cells (LSCs). A fraction of LSCs persist in a quiescent state and are seen in patient with CML in cCyR. It is believed that they are responsible for CML relapse upon discontinuation of imatinib therapy.

2.1 Newer agents in CML treatment

New drugs have been developed with special interest in agents active in highly TKI-resistant CML (Table 1).

3. Multiple myeloma

Multiple myeloma (MM) is a B-cell neoplasm that is characterized by clonal proliferation of terminally differentiated plasma cells. Clinical features include bone disease, hypercalcemia, cytopenias, and renal dysfunction. Our understanding of this disease has improved significantly in the past decade and has lead to the development of novel targeted therapies. The interaction between MM cells and their microenvironment is the subject of intense research and several novel targets have emerged(Hideshima, Mitsiades et al. 2007).

Drug	Study Phase	Comments	Clinical trial*
Panotinib	II	Third generation TKI which acts against T315I mutation	NCT01207440
Danusertib	II	Inhibits Aurora kinase and BCR-ABL1 (includes T315I mutation)	NCT00335868
XL-228	I	Inhibits Aurora kinase and BCR-ABL1 (includes T315I mutation)	NCT00464113
AT-9283	I	Inhibits Aurora kinase and BCR-ABL1 (includes T315I mutation)	NCT00522990
DCC-2036	I	Switch pocket inhibitor	NCT00827138
BMS-214662	I	Farnesyl transferase inhibitor	NCT00006213
Panobinostat	I/II	Histone deacetylase inhibitor	NCT00686218
Omacetaxine	I/II	Homoharringtonine formulation- disrupts protein synthesis	NCT00462943 NCT00375219 NCT00006364

* Clinicaltrials.gov accessed on 4/30/11

Table 1. Lists the newer promising agents currently in preclinical or clinical phase of development for treatment of CML.

3.1 Intracellular and nuclear targets
3.1.1 Proteasome inhibitors

The proteasome is an abundant catalytic complex that is found in both the nucleus and cytoplasm of eukaryotic cells (Adams 2004). Its function is to degrade intracellular proteins,such as the cyclins, caspases, BCL2 and NF-κB, which mediate cell cycle progression and apoptosis. The mechanisms by which malignant cells are more susceptible to proteasome inhibition than normal cells are not completely understood. One explanation is that many types of malignant cells rapidly proliferate and have one or more aberrant cell-cycle checkpoints. These cells might accumulate defective proteins at a higher rate than normal cells, which increases their dependency on the proteasome as a disposal mechanism. Inhibition of proteasome function would lead to a progressive accumulation of these proteins and could trigger apoptosis. In addition, NF-κB activation pathway has been associated with MM and has been linked to drug resistance. Proteasome inhibition might make malignant cells more sensitive to apoptosis by death-inducing ligands (Jeremias, Kupatt et al. 1998).

Bortezomib (Velcade, Millenium Pharmaceuticals, Country) was the first proteasome inhibitor to be widely used in the management of MM. It is a boronic acid dipeptide that reversibly inhibits chymotryptic-like activity of the proteasome and blocks the NF-κB pathway. Bortezomib treatment also leads to downregulation of transcripts that are associated with growth and survival pathways (e.g. IGF-1 pathway) and upregulation of transcripts involved in both of the main pro-apoptotic pathways (Mitsiades, Mitsiades et al. 2002). In MM cells, bortezomib inhibits DNA repair and induces p53 by phosphorylation

and degradation of MDM2, through activation of caspase-3 by caspase-8. Bortezomib also inhibits MM- bone marrow stromal cell (BMSC) interactions(Mitsiades, Mitsiades et al. 2002), expression of phosphorylated VEGF-induced caveolin-1, ICAM-1, VCAM-1(Kastritis, Charidimou et al. 2009).

The antimyeloma activity of bortezomib was confirmed in a phase II study (CREST) in relapsed or refractory MM patients (Richardson, Barlogie et al. 2003; Jagannath, Barlogie et al. 2008). Bortezomib was administered with or without dexamethasone and a response was seen in 35% with a complete response (CR) in 7 patients and a near complete response (nCR) in 12 patients. Subsequently a phase III randomized study in relapsed MM (Richardson, Sonneveld et al. 2005) demonstrated a RR of 43% with 9% CRs. These findings led to the approval of bortezomib by the FDA for relapsed or refractory myeloma. Studies of bortezomib in front line setting have demonstrated higher RR (Harousseau, Attal et al. 2010) in the bortezomib combination arm and continued to remain higher after transplant as long as patients have achieved at least very good partial response (VGPR). This and other studies have found that bortezomib remains superior in patients with high-risk disease (elevated β2-microglobulin, deletion of chromosome 13, t (4;14), and del p53) (Cavo M 2007; Harousseau, Attal et al. 2010). Bortezomib based regimens have also been found to be effective as front line treatments in transplant ineligible patients (Mateos, Hernandez et al. 2006).

As more data emerged about the effects of proteasome inhibition on MM cells several studies of combining bortezomib with other agents were designed. These were initially studied in the preclinical setting based on synergistic rationale and several of these are now being studied in the clinical setting.

Several second generation proteasome inhibitors are currently being studied for their role in treatment of MM. Carfilzomib is an irreversible proteasome inhibitor that binds to β5 subunit of the 20S proteasome (Kuhn, Chen et al. 2007). Multiple pathways are implicated in the programmed cell death of MM cells when exposed to carfilzomib (Kuhn, Chen et al. 2007). Carfilzomib has been studied in relapsed/refractory multiple myeloma patients demonstrating a 26% RR (S. Jagannath 2009). In another phase II study comparing bortezomib exposed and naïve patients, the naïve patients had a greater RR (57%) (R. Vij 2009).

Other proteasome inhibitors CEP 18770, Marizomib and MLN 9708 are also currently being evaluated in phase I and II studies (www.clinicaltrials.gov ; Chauhan, Catley et al. 2005; Piva, Ruggeri et al. 2008). Marizomib (NPI-0052) is an orally active proteasome inhibitor that acts by a different mechanism to inhibit the proteasome. Marizomib has been shown to be a more potent inhibitor of the NF-κB and other cytokines (Chauhan, Catley et al. 2005) than Bortezomib. It interferes with the chymotryptic-like, tryptic-like and caspase-like proteolytic activity of the proteasome, while bortezomib only interferes with the chymotryptic-like. It has also been shown to overcome bortezomib resistance both *in vitro* and *in vivo*. Studies are currently evaluating Marizomib as a single agent as well as in combination with bortezomib where a synergistic effect has been seen (Chauhan, Singh et al. 2008).

3.1.2 Immunomodulatory drugs

Immunomodulatory drugs (IMids) including thalidomide (Thal) and lenalidomide (Len) are commonly used in the treatment of MM (Rajkumar 2011). Multiple mechanisms have been proposed including effects on angiogenesis, cytokine production, direct antineoplastic

effects, anti-inflammatory effects, sensitization of MM cells to apoptosis and interaction with bone and micro-environment (D'Amato, Lentzsch et al. 2001; Mitsiades, Mitsiades et al. 2002). IMiDs may have direct antineoplastic effects by blocking signaling through NF-κB signaling, which is universally activated in MM cells and may induce apoptosis via the caspase-8/death receptor pathway (Lacy 2011). Pamilidomide and Len also cause cell cycle arrest in plasma cells by p21 WAF-1 activation, which is p53 independent, suggesting possible efficacy in cancer with p53 mutation and deletion (Escoubet-Lozach, Lin et al. 2009). They also have potent immunomodulatory properties including augmentation of natural killer cell activity and stimulation of cytotoxic T cells (Haslett, Corral et al. 1998; Corral, Haslett et al. 1999).

Thal is a synthetic glutamic acid derivative that was the first agent in this class to be used to treat MM because of its antiangiogenic properties. In relapsed myeloma, Thal and dexamethasone have RR of 40 to 50% (von Lilienfeld-Toal, Hahn-Ast et al. 2008). Len was approved by the FDA based on results from phase III studies that showed a combination of Len and high dose dexamethasone was superior to dexamethasone alone (Dimopoulos, Spencer et al. 2007; Weber, Chen et al. 2007). The RR was 60% in the Len group as compared to 24% in the placebo group. A significant difference was also seen in the time to progression (TTP) (11.3 months vs 4.7 months) and OS (HR 0.66). Comparison of Len with high or low dose dexamethasone showed that the low dose dexamethasone is safer and associated with improved survival in patients with newly diagnosed MM (Rajkumar, Jacobus et al. 2010). A subsequent phase I/II study evaluated the combination of Len, bortezomib and dexamethasone in newly diagnosed MM and reported partial response (PR) was 100% with 74% achieving a VGPR. With a median follow up of 21 months, estimated 18-month progression free survival (PFS) and OS for the combination treatment with/without transplantation were 75% and 97% respectively. A phase III trial evaluating Len /dexamethasone vs bortezomib/ Len /dexamethasone as induction treatment in newly diagnosed MM patients who are not candidates for transplant is currently underway (www.clinicaltrials.gov). A combination of bortezomib, dexamethasone, Len and cyclophosphamide is being studied in a phase I/II trial (EVOLUTION) (Kumar, Flinn et al. 2010). The overall RR in the phase I portion of this study was 96% with a 68% VGPR or better. Len has also shown benefit as maintenance treatment after transplant (Michel Attal 2010; Philip L. McCarthy 2010). In the CALGB trial patients who were randomized to receive Len (10mg daily) had a median TTP of 42.3 months vs. 21.8 in the placebo arm.

Pomalidomide is a new Thal derivative and has been shown to be the most potent IMiD (Lacy 2011). In addition to mechanisms mentioned above, pomalidomide may have a role in preventing or treating myeloma bone disease via effects on osteoclasts (Anderson, Gries et al. 2006). A phase II study using pomalidomide and dexamethasone in a relapsed/refractory multiple myeloma showed a RR of 63% (33% CR or VGPR) (Lacy, Hayman et al. 2009). The median PFS in this study was found to be 11.6 months irrespective of risk factors. This and other studies seem to suggest that pomalidomide is active in patients that are refractory to Len and those who have high risk molecular markers.

3.1.3 Heat shock protein 90 (HSP 90) inhibitors

HSP90 is a molecular chaperone that is induced in response to cellular stress and stabilizes client proteins involved in cell cycle control and proliferative/anti-apoptotic signaling. It facilitates the folding and stability of numerous signaling molecules that control the growth

and survival of cancer cells (Whitesell and Lindquist 2005). HSP 90 is a key molecular chaperone for signal transduction proteins critical to MM cell growth and survival and drug resistance. MM cells produce a large quantity of immunoglobulins that are folded into tertiary structures in the endoplasmic reticulum. HSP90 plays a large role in chaperoning these proteins into formation and disposing of misfolded proteins. HSP90 inhibitors interrupt this chaperoning activity, which leads to accumulation of misfolded proteins, endoplasmic reticulum stress, and ultimately apoptosis (Davenport, Moore et al. 2007; Mitsiades, Hideshima et al. 2009; Chanan-Khan, Borrello et al. 2010).

Tanespimycin (KOS-953) is one of the HSP90 inhibitor and acts mainly through the inhibition of ATPase activity of HSP90. HSP90 inhibition increases the bortezomib induced apoptosis in MM cells by blocking the HSP90 stress response. Preclinical data has shown that tanespimycin may also be protective against the peripheral neuropathy associated with bortezomib. A phase I/II study evaluated bortezomib followed by tanespimycin in relapsed/refractory MM (P. G. Richardson 2009) and reported RR were 41%, 20% and 14% in the bortezomib-naïve, bortezomib-pretreated and bortezomib-refractory patients respectively. Several other HSP90 inhibitors are currently in early phase trials to evaluate their response in myeloma.

3.1.4 HDAC inhibitors

Eukaryotic DNA is packed in a high level structure called chromatin. Expression of genes is controlled by the interaction between the negatively charged phosphate groups on DNA and the positively charged amine groups on the lysine and arginine amino acids on histone terminal tails. The N-e-acetylation of lysine residues found in histones is equilibrated by two enzymes: the histone acetyl transferases (HAT) and the histone deacetylases (HDAC). HDAC inhibitors result in an increase in acetylation of histones which in turn promotes the re-expression of silenced regulatory genes. These compounds represent a family of small molecule-based anti-cancer therapies.

Currently several HDAC inhibitors are being studied as single agents or in combination with other agents mainly bortezomib and Len. Vorinostat is an oral HDAC inhibitor that is currently being used in the treatment of T-cell lymphoma. It downregulates IGF-1 and IL6 signaling pathways as well as DNA synthesis and repair enzymes (Mitsiades, Mitsiades et al. 2004). Vorinostat is also being studied in combination with bortezomib based on preclinical studies which suggest synergistic anti-MM activity.(Mitsiades, Mitsiades et al. 2004). Phase I studies combining bortezomib and vorinostat have shown (Badros, Burger et al. 2009) RR of 42% including 3 PRs among 9 bortezomib refractory patients. Further studies with vorinostat in combination with other agents are currently ongoing.

Panobinostat (LBH589) is a potent pan-deacetylase inhibitor that disrupts aggresome and HSP 90 function via inhibition of HDAC6, promoting cytotoxic misfolded protein aggregates and MM cell death. It is currently being tested in combination with other therapies for relapsed/refractory MM. In a phase Ib trial responses were observed in 68% of patients across all cohorts and in 62% of bortezomib refractory patients. (M. Alsina 2010). Several other phase I and I/II trials have shown similar responses in relapsed/refractory MM in combination with Len and melphalan (M Mateos 2010) prednisone and Thal (Massimo Offidani 2010). Currently phase II trials are ongoing comparing a combination of Panobinostat/Bortezomib/Dexamethasone   vs   Bortezomib/Dexamethasone   in relapsed/refractory MM. Overall panobinostat in combination with other agents has shown encouraging anti-myeloma activity however further studies are needed to establish its role in treatment of MM.

Other HDAC inhibitors currently being evaluated in the treatment of MM are romidepsin, belinostat, ITF2357 and AR 42.

3.1.5 AKT

The Phosphoinositide 3 Kinase (PI3K)/protein kinase B(AKT) pathway is a central signaling pathway in several cellular functions including proliferation, growth, survival and migration. AKT is activated by PI3K and in turn activates several downstream targets. AKT activation has been reported to induce growth and survival advantage to MM cells through GSK-3β and mTOR phosphorylation. AKT activation has been shown to be associated with advanced stage and poor prognosis in MM patients and also resistance to dexamethasone in MM cells. Targeting the PI3K/AKT pathway is being studied in hematological malignancies (Kawauchi, Ogasawara et al. 2009).

Perifosine (KRX-0401) is a synthetic novel oral alkylphospholipid that inhibits both constitutive and cytokine induced AKT activation and januskinases (JNK) activation leading to apoptosis of MM cells including those adhering to bone marrow stromal cells (BMSC) (Mitsiades, Hideshima et al. 2009). In a phase I/II study adding perifosine to bortezomib and dexamethasone treatment showed an RR of 38% and OS of 16 months in the bortezomib-refractory group and an RR of 55% and a median OS that is not reached in the bortezomib-relapsed group (Paul Richardson 2009). Currently there is a phase III trial recruiting patients with MM pretreated with bortezomib, to be randomized to bortezomib-dexamethasone and perifosine or placebo (NCT01002248).

3.1.6 Mammalian target of rapamycin (mTOR)

The mammalian target of rapamycin (mTOR) is an intracellular kinase that controls the production of proteins through regulation of their translation. mTOR is activated by AKT and regulates cell growth, proliferation, motility, survival and metabolism. mTOR exerts its downstream effects through the formation of protein complexes called mTORC1 and mTORC2. The PI3K/AKT pathway is commonly activated in human cancer and active AKT promotes mTORC1 signaling by phosphorylating and inhibiting the tuberous sclerosis1/2 (TSC1/TSC2) negative regulatory complex(Dowling, Topisirovic et al. 2010). mTOR acts as a neoplastic switch that is frequently turned on by many mutations found in cancer, and its inhibition offers a promising target.

Temsirolimus is an analogue of the rapamycin that acts by binding to FKBP-12, an intracellular protein, and the FKBP-12-temsirolimus complex inhibits mTOR activity in the PI3K-AKT pathway. In addition to renal cell carcinoma temsirolimus is being investigated in MM and other cancers. A phase II study (Farag, Zhang et al. 2009) reported an overall RR of 38% (1 PR, 5 MR). Another phase I/II study reported 33% overall RR combining temsirolimus with bortezomib (Ghobrial, Weller et al. 2011). Other mTORs including everolimus and ridaforolimus are currently being studied in MM (www.clinicaltrials.gov).

Emerging data has shown that rapamycin analogs do not appear to be effective as monotherapies (Dowling, Topisirovic et al. 2010). Rapamycin treatment leads to hyperactivation of AKT through loss of the mTORC1/S6k1/IRS-1/PI3K negative feedback loop. In addition to this mTORC2 is rapamycin insensitive and is known to cause AKT phosphorylation. A majority of the first generation mTOR inhibitors that do not inhibit mTORC2 are thus not as effective as previously thought, but their use in combination with other agents can overcome these resistance mechanisms. This serves as the rationale for

Target	Drug	Study phase	Comments
Farnesyl transferase	Tipifarnib (Zarnestra)	II	FTI inhibitors prevent the farnesylation of Ras. Preclinical models have shown a synergism with bortezomib.
Bcl2	Obatoclax ABT737	I/II Preclinical	Bcl2 prevents cell death by inhibiting adapter molecules involved in the activation of caspases in intrinsic pathway. It is overexpressed in most human tumor types.
Aurora A Aurora B	MLN 8237 ENMD-2076 TAK 901	I/II I I	The aurora kinases regulate cell cycle transit from G2 through to cytokinesis. Aurora kinase inhibitors have been shown to inhibit MM cells.
P38 MAPK	SCIO 469	II	MAPK is a signaling protein that is important in cell proliferation. In combination with bortezomib an ORR of 32% with 9% stable disease in rel/ref MM.
Kinesin spindle protein	ARRY 520	I/II	KSP is required for cell cycle progression through mitosis. KSP inhibition arrests cells in mitosis, resulting in cell death and KSP inhibitors target proliferating cells.
Multiple kinases	Plitidepsin (Aplidin) Curcumin Sorafenib	III II I/II	Plitidepsin is a cyclodepsipeptide which induces MM cell death by activation of p38 and c-jun signaling as well as caspase activation. A phase II study showed 15% ORR.
CDK	Dinaciclib PD 0332991 Flavopiridol SNS-032 Seliciclib	I I/II I/II I I/II	Cyclin dependant kinases (CDKs) are a family of protein kinases that play a vital role in cell cycle regulation. Cyclins D1, D2 and D3 are dysregulated in all MM cells. CDK inhibitors target multiple CDKs as well as other targets including RNA polymerase II or GSK-3β. CDKIs are being testes as single agents or in combination in MM.
PKC β	Enzastaurin	II	
MEK 1/2	Selumitinib (AZD6244)	II	MEK/ERK pathway activation in MM is critical for cell growth and survival. AZD6244 has been shown to target both MM cells and osteoclasts
Casein Kinase 2	CX-4945	I	
Telomerase	GRN163L	I	GRN163L is an antisense oligonuleotide that binds to, and competitively inhibits telomerase. This leads to telomerase shortening, cessation of MM cell growth, and promotion of apoptosis.
IKK	RTA 402 PS 1145	I Preclinical	
eIF5A	SNS01-T	Preclinical/I	

Table 2. Agents targeting intracellular and nuclear molecules.

combining mTOR inhibitors with AKT inhibitor perifosine which has shown enhanced activity in MM cells (Cirstea, Hideshima et al. 2010). Other combinations of mTOR inhibitors with MAPK inhibitors or RAF/VEGF inhibitors are currently being tested in the clinical setting. Newer mTOR inhibitors that have activity against mTORC2 may represent agents that could be used in combination with other anti-myeloma agents in the future.

Several other intracellular and nuclear targets are being studied in different stages for MM. Some of these are in clinical trials (plitidepsin) while others are still in the preclinical phase (IκB kinase (IKK) inhibitors or SNS01-T). More agents that are being tested in multiple myeloma are shown in table 2.

3.2 Cell surface receptors, growth factors and growth factor receptors targets
3.2.1 EGFR

The epidermal growth factor (EGFR) is a member of the ErbB family of receptor tyrosine kinases and its role in carcinogenesis has been established. Upon ligand binding the EGFR homo or heterodimerizes, which in turn stimulates the tyrosine kinase activity and initiates cell signaling pathways including mitogen activated protein kinase (MAPK) pathway and the PI3 kinase pathway (Mendelsohn and Baselga 2006). EGFR has been shown to be expressed on malignant plasma cells of MM and its microenvironment. Inhibiton of EGFR signaling has shown to induce apoptosis in MM cells (Mahtouk, Jourdan et al. 2004; Mahtouk, Hose et al. 2005). Cetuximab is a chimeric anti-EGFR antibody that inhibits EGFR-ligand interaction and induces cell cycle arrest, apoptosis, and antibody-dependant cellular cytotoxicity (ADCC) (Boll, Eichenauer et al. 2010). A phase II trial is currently undergoing to evaluate dexamethasone with or without cetuximab in relapsed/refractory MM (Boll, Eichenauer et al. 2010).

3.2.2 IL6

IL6 is an inflammatory cytokine that activates Jak/STAT pathway by binding to its receptor (IL6R). It acts as an antiapoptotic factor for MM cells and also confers drug resistance within the bone marrow microenvironment. IL6 also stimulates osteoclastogenesis thereby contributing to the development of osteolytic lesions. Siltuximab (CNTO 328) is a chimeric monoclonal antibody that is derived from the fusion of the murine variable IL6 binding region with human IgG constant domain. Preclinical studies have shown that CNTO 328 enhances the cytotoxic effects of bortezomib by activation of caspases 3, 8 and 9 (Voorhees, Chen et al. 2007). A phase II study combining CNTO 328 and dexamethasone in relapsed/refractory MM has shown 57% RR (3CR, 9PR). Antibodies directed against the IL6 receptor are also currently being studied in MM.

3.2.3 CS1

CS1 is a cell surface glycoprotein belonging to immunoglobulin gene superfamily that is highly expressed on MM cells (Hsi, Steinle et al. 2008). The role of CS1 is not clear but it may promote and supports MM cell adhesion to BMSCs. Anti-CS1 staining was seen in all plasmacytomas and bone marrow biopsies. More importantly CS1 staining is not seen on normal tissues including CD34 cells. Elotuzumab (HuLuc63) is a humanized monoclonal antibody that has shown to induce significant anti-myeloma activity both *in vitro* and *in vivo* (Hsi, Steinle et al. 2008; Tai, Dillon et al. 2008). A phase I/II study evaluating elotuzumab with Len and low dose dexamethasone in relapsed/refractory MM has shown that the

combination is relatively safe and a RR of 82% (64%PR, 18% VGPR) (S. Lonial 2010). Another phase I study combining elotuzumab with bortezomib (A. J. Jakubowiak 2010) demonstrated a RR of 60%.

3.2.4 CD40

CD40 is a transmembrane protein belonging to the tumor necrosis factor -α (TNFα) family and is highly expressed on the surface of MM cell lines and primary MM cells (Westendorf, Ahmann et al. 1995). Binding of CD40 on MM cells with its ligand ,CD40L, upregulates the expression of adhesion molecules (e.g. LFA-1 and VLA-4) which further enhances the adhesion of MM cells to BMSCs as well as IL-6 and vascular endothelial growth factor (VEGF) secretion from BMSCs (Hideshima, Mitsiades et al. 2007). CD40 activation promotes MM cell growth and migration via PI3K/AKT/NF κB signaling. Anti CD40 monoclonal antibodies (SGN-40, CHIR-12.12) have shown anti-MM activity *in vitro* and *in vivo* (Hayashi, Treon et al. 2003; Tai, Catley et al. 2004). A phase I study of dacetuzumab (SGN-40) reported 20% stable disease (SD). Further trials using dacetuzumab in combination with other agents including Len are currently underway (Edward Agura 2009).

Several other agents directed against cell surface receptors, growth factors and growth factor receptors are listed in table 3.

4. Targeted therapy in lymphoma

Despite remarkable advances in diagnostic techniques and treatment, lymphoma remains leading cause of cancer-related mortality. Since US Food and Drug Administration (FDA) approval in 1997, rituximab has been the mainstream of treatment for non-Hodgkin's Lymphoma (NHL) expressing CD20 antibody on their surface. The surface expression of CD20 on B cell lymphoma, and the fact that most NHL's are B cell has provided development of this and many other monoclonal antibodies (mAB) in treatment of this group of malignancies.

To-date there are about six mAB based treatments for hematologic malignancies that have been approved by Food and Drug Administration (FDA) in the United States. These mAB treatments have improved outcomes and reduced toxicity compared to more conventional thermotherapy regimens. In spite of recent advances in mAB development, current treatments are not optimally effective; with relapse and resistance to chemotherapy or even mAB's seen commonly and the risk of secondary malignancies is an ongoing concern. Due to upcoming more sophisticated and modern molecular techniques new monoclonal antibodies targeting CD3, CD4, CD8, CD20, CD22, CD19, CD40, CD52, CD 74 and HLA Drβ has been developed, but only antibody to CD20 on B cells and CD52 on T cells are broadly used in clinical practice.

4.1 Rituximab
4.1.1 Diffuse large B-Cell lymphoma

Diffuse Large B-Cell Lymphoma (DLBCL) is the most frequent subtype of NHL in all countries around the world and all age groups (Jaffe ES 2001). This aggressive lymphoma is potentially curable, but carries a high risk of relapse. Addition of rituximab (R) to standard

Target	Drug	Study phase	Comments
TRAILr	Mapatumumab	II	A humanized mAb for TNF-related apoptosis-inducing ligand receptor being studied in combination with bortezomib because of its ability to induce apoptosis.
VEGF, VEGFr	Bevacizumab Vandetanib	II II	Angiogenesis plays a crucial role in MM regulated by interactions between the MM cells and the BM microenvironment.
IGF1, IGF1R	AVE 1642	I	IGF signaling pathway is important in tumor growth invasion and metastasis through the Ras/Raf/MEK and PI3K/AKT pathways. Targeting this pathway is difficult due to the cross reactivity with insulin receptors.
Hedgehog	BMS 833923	Ib	BMS 833923 is a small molecule inhibitor of Smoothened (SMO), a component of the hedgehog (Hh) pathway that plays a role in cell differentiation and proliferation. A multiple ascending dose (MAD) study is underway.
CS1	Elotuzumab (HuLuc63)	I/II	
CD 56	BB-10901 IMGN901	I I	CD 56 is a membrane glycoprotein that is expressed on 70-90% of MM cells. Humanized mAb linked to DM1, a cytotoxic maytanisinoid are being studied in combination with other drugs.
PD-1	CT 011	II	
Tyrosine kinase inhibitors.	Dasatinib Dovitinib (TKI 258) Sunitinib	II II II	Several targets of TKIs including Src family kinases, PDGFR and cKIT have shown some role in MM pathology and these drugs are being studied as single agents or in combination with other agents. Dovotinib is an inhibitor of the FGF-3 receptor that is involved in 10-20% MM patients with t(4;14).
KIR	IPH 2101	II	
RANKL	Denosumab	I/II	
DKK	BHQ880	I/II	DKK is a soluble Wnt pathway antagonist that is secreted by MM cells and inhibits osteoblastic activity and its serum level correlates with osteolytic lesions.
GM2	BIW 8962	I/II	
CD 38	Daratumumab	I/II	
MUC1	ImMucin	I/II	
CD 74	Milatuzumab	I/II	
BAFF	LY2127399 AMG523	I/II Preclinical	B cell activating factor (BAFF) is derived from stromal cells and osteoclasts and its inhibition reduces tumor burden and osteolytic lesions in preclinical studies.
CXCR 4	BKT 140	I/II	
CD 138	BT 062	I/II	CD 138 is a heparin sulfate proteoglycan that serves as a receptor for EGF ligands and is overexpressed on MM cells.

Table 3. Agents targeting cell surface antigens, growth factors/cytokines and growth factor receptors.

CHOP (cyclophosphamide, hydroxydaunorubicin (doxorubicin), oncovin (vincristine), and prednisone) has transformed outcome of DLBCL, and increased cure rate by about 20%.

A: Previously untreated DLBCL

The first study was reported by Coiffier et al (Coiffier, Lepage et al. 2002) and was recently updated (Coiffier, Thieblemont et al.) in 2010. In this French study, patients with untreated DLBCL were randomized to either CHOP or R-CHOP. Event free survival (EFS) was significantly improved with addition of R. Higher CR or unconfirmed complete response (uCR) was achieved in R arm (76% Vs 63%). Survival also improved by 13% (70% compared to 57%) at 2 years in the R arm. This benefit was independent of international prognostic index (IPI) and age. Recent update of this study confirmed improvement in PFS and OS at 10years in the R combination arm (PFS 36.5%, vs 20%, OS 43.5% vs 27.6%). (Coiffier, Thieblemont et al.)

ECOG 4494 (Habermann, Weller et al. 2006) trial evaluated the role of R in induction and maintenance treatment of untreated DLBCL patients. Two year failure free survival (FFS) rate was significantly higher in maintenance R arm (MR) (76% vs 61%) however there was no significant OS benefit. In addition patients who received R in induction phase did not benefit from MR. In a secondary analysis, patients who received R-CHOP as induction had longer three year FFS (52% vs 39%) as well as OS (67% vs 58%).

Role of R in good-risk younger patients was reported by the Mabthera International Trial group (Pfreundschuh, Trumper et al. 2006). In that trial patients assigned to R-chemotherapy arm had significantly improved three year event free survival (EFS) (79% vs 59%) and OS (93% vs 84%). On long term follow up there was continued benefit in EFS (Pfreundschuh M 2010). Data in younger patients with high risk features is lacking, simply due to fact that this patient population is best served with autologous transplant in first CR (Milpied, Deconinck et al. 2004). S9704 (South West Oncology Group), a phase III randomized trial addressing that question, has completed accrual and results are expected to be presented soon.

B. Relapsed DLBCL

R has improved response rates of salvage regimens like ICE (ifosfamide-carboplatin-etoposide) (Kewalramani, Zelenetz et al. 2004) and DHAP (cisplatin-cytosine arabinoside-dexamethasone) (Witzig, Geyer et al. 2008). A recent trial evaluated R-ICE vs R-DHAP followed by autologous stem-cell transplant (ASCT) and then again randomized to R maintenance or observation (Gisselbrecht, Glass et al.). R-ICE or R-DHAP had similar 3 years EFS and OS. Prior R treatment, early relapse (<12 months) and higher IPI (2 or higher) have been shown to affect 3yrs EFS, PFS and OS. Data from R maintenance part of this trial is still maturing and may provide insight for future treatments.

4.1.2 Follicular lymphoma

Follicular lymphomas (FL) are considered incurable with standard chemotherapeutic options (Cheson et al 2007). Multiple phase III trials have shown improvement in PFS as well as OS in low-grade B cell lymphoma when treated with R.

Initial study by Czuczman et al reported 95% overall RR (55% CR, 40% PR). 74% patients remained in remission at the end of median follow up of 29 months (Czuczman et al 1999). German Low-Grade Lymphoma Study Group (GLSG) conducted a larger study with untreated advanced-stage FL randomized to R-CHOP versus CHOP (Hiddemann et

al 2005). Overall RR was higher in R-CHOP arm compared to CHOP only arm (96% vs 90%, p=0.011), though CR rates were not statistically significant (20% vs 17%). Importantly, after median follow up of 18 months, 28 patients relapsed in R-CHOP arm compared to 61 patients in CHOP arm, resulting in significant risk reduction by 60% and longer time to failure (p<0.001), as well as longer duration of response (p=0.001). This benefit was extended to all subgroups irrespective of IPI status and age. R in combination with interferon and chemotherapy in patients with high tumor burden was reported to have improved disease control with fewer treatments(Salles et al 2008). East German Study Group Hematology and Oncology study reported improved survival with R combination (Herold, Haas et al. 2007).

Based on the above trials R-CVP or R-CHOP has been established as a standard of care for advanced stage follicular lymphoma. R continues to be evaluated in combination with new agents.

GLSG reported significantly higher overall RR, PFS and 2 year survival rates in combining R with chemotherapy in patients with relapsed/refractory FL (Forstpointner, Dreyling et al. 2004). Another phase III trial reported similar results (van Oers et al 2006)- superior overall RR (85.1% vs 72.3%; P < .001) and CR rate (29.5% vs 15.6%; P < .001).

Recently, PRIMA study reported R as maintenance therapy, after induction treatment, improved CR rates and PFS however there was no difference in OS (Salles, Seymour et al.). Similar findings were reported in MAXIMA trial phase IIIb update at ASH 210 meeting (Fao R et al). These two trials have established a role for maintenance R in improving RR and FFS however there was no improvement in OS.

The Watch and Wait study is a randomized phase III trial which enrolled patients with asymptomatic, non-bulky stage II, III and IV FL (Ardhesna et al)(Kirit M Ardeshna 2010). Primary end point of this study was to determine time to initiation of new systemic therapy, and quality of life. 462 Patients were randomly assigned with ratio of 1:1:1 to watchful waiting (arm A), R 375mg/m² weekly for four weeks (arm B) or R 375mg/m² weekly for 4 weeks followed by MR every 2 months for 2 years (arm C). Median follow-up was 34 months at the time of analysis. At three years, 49% of patients in watchful waiting did not receive any treatment, compared to 80% in R single agent (arm B) and 91% in MR (arm C). After three years, 30% of patients in watchful waiting group had not progressed compared to 60% in R single agent (arm B) and 81% in MR (arm C). Further follow-up did not reveal any difference in survival in either of the arms. Dr. Ardeshna concluded that R significantly improved both the time to initiation of new therapy and PFS.

4.1.3 Rituximab in other lymphomas

Rituximab has been evaluated in other lymphomas. R was added to hyper-CVAD (hyperfractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone) alternating with high-dose methotrexate/cytarabine regimen for newly diagnosed patients with mantle cell lymphoma (MCL), Burkitt lymphoma and mature B-cell acute lymphoblastic lymphoma (Fayad, Thomas et al. 2007). Overall RR for MCL was 97% (CR/uCR 87%); 5 year FFS and OS were 48% and 65% respectively after median follow-up of 4.8 months. After median follow-up of 22 months overall RR for Burkitt's lymphoma was 97% (CR 86%) with estimated 3-year OS, disease-free survival and EFS of 89%, 88% and 80% respectively (Fayad, Thomas et al. 2007). R also has shown activity in patients with relapsed indolent lymphoma or MCL in conjunction with bendamustine in a phase II

trial (Robinson, Williams et al. 2008). Overall RR was 92% (CR 41%, uCR 14%, and PR 38%). Median duration of response and PFS were 21 months (95% CI, 18 to 24 months) 23 months (95% CI, 20 to 26 months) respectively. Outcomes were similar for patients with indolent or mantle cell histologies (Robinson, Williams et al. 2008). Recently, R with bendamustine has shown significant RR including CR, as well as rapid and durable responses in patients with Waldenstorm macroglobulinemia (Treon, Ioakimidis et al. 2009).

4.2 mTOR inhibitors

Details regarding the pathway are mentioned above in MM part of this chapter. MCL is an aggressive NHL with cyclin D1 over-expression, which remains target for these mTOR inhibitors. The rapamycin analogues, everolimus and temsirolimus, are approved for treatment of renal cell cancer and have shown activity in lymphoma in pre-clinical models (Jundt, Raetzel et al. 2005).

A phase II study evaluated role of everolimus as a single agent in patients with relapsed aggressive lymphoma (DLBCL 61%, MCL 25%, FL-III 10%)(Witzig, Reeder et al.). Overall RR was 30% (20PR/3uCR). Median duration of response was 5.7 months, and 5 patients remained disease free at 12 months. A study is currently recruiting patients to determine whether everolimus plus R is safe and effective in patients with relapsed or refractory DLBCL (NCT00869999) .

Temsirolimus was initially studied in relapsed MCL as a single agent (Witzig, Geyer et al. 2005). ORR was 38% (3% CR, 35% PR). The median time-to-progression was 6.5 months; with duration of response of 6.9 months. A recent phase III study randomized 162 patients with relapsed or refractory MCL to 1:1:1 to receive one of two temsirolimus regimens: 175 mg weekly for 3 weeks followed by either 75 mg (175/75-mg) or 25 mg (175/25-mg) weekly, or investigator's choice therapy from prospectively approved options (Hess, Herbrecht et al. 2009). Overall RR was 22%, 6% and 2% in 175/75-mg, 175/25-mg, and investigator's choice groups, respectively. Median PFS was 4.8 (175/75-mg), 3.4 (175/25-mg), and 1.9 months (investigator's choice groups, p=0.0009 vs 175/75 mg). Patients treated with temsirolimus 175/75-mg had significantly longer PFS than those treated with investigator's choice therapy (P = .0009; hazard ratio = 0.44); those treated with temsirolimus 175/25-mg showed a trend toward longer PFS (P = .0618; hazard ratio = 0.65)(Hess, Herbrecht et al. 2009). Overall RR was significantly higher in the 175/75-mg group (22%) compared with the investigator's choice group (2%; P = .0019). Median OS for the 175/75-mg, 175/25-mg, and investigator's choice groups was 12.8, 10 and 9.8 months respectively at the time of last update (Hess, Herbrecht et al. 2009).

Deforolimus is a novel mTOR inhibitor which was studied in relapsed/refractory hematologic malignancies (Rizzieri, Feldman et al. 2008) and is undergoing clinical studies (NCT00086125).

Preclinical studies have shown efficacy of mTOR inhibitors in Waldenstrom macroglobulinemia (WM), this was followed by a phase II trial (Ghobrial, Gertz et al.). Overall RR of 70% (42% PR, 28% minimal response, 0 CR) with estimated PFS at 6 and 12 months of 75% and 62% were reported. Everolimus was also studied in relapsed Hodgkin's lymphoma (HL) (Johnston, Inwards et al.). 19 patients with relapsed HL received everolimus with overall RR of 47% (1CR, 8PR) and a median duration of response of 7.1 months (Johnston, Inwards et al.).

4.3 Radioimmunotherapy

The efficacy of R can be augmented by "arming" the antibody with a radionuclide, toxin, or chemotherapeutic agent. In case of lymphomas, radioimmunotherapy (RIT) using CD20-targeted immunoconjugates was developed. Two available RITs are: tositumomab/iodine I-131 tositumomab (Bexxar) and Yttrium-90 –Labeled Ibritumomab Tiuxetan (Zevalin). Ibritumomab, the murine IgG1 anti-CD20 antibody that is the parent of the engineered chimeric antibody R, targets the same epitope on the CD20 antigen.

A large randomized phase III trial compared R to yttrium-90 (90Y) ibritumomab tiuxetan in 143 patients with relapsed or refractory low-grade, follicular, or transformed CD20(+) transformed NHL (Witzig, Gordon et al. 2002). Overall RR was 80% for the ^{90}Y ibritumomab tiuxetan group versus 56% for the R group (P =.002). CR was higher in the ^{90}Y ibritumomab tiuxetan arm compared to R groups (30% vs 16%, p=0.04). An additional 4% achieved an unconfirmed CR in each group. Median duration of response (14.2 mo vs 12.1 mo, p=0.6) or TTP (11.2 mo vs 10.1 mo, p=0.30) were not significantly different.

Another RIT ^{131}I-Tositumomab was evaluated in treatment-naïve advanced stage FL (Kaminski, Tuck et al. 2005). Overall RR was 95% with CR of 75%. PFS was 59% and median PFS was 6.1 years with median follow-up of 5.1 years. Of 57 patients who had a CR, 40 remained in remission for 4.3 to 7.7 years. Southwest Oncology Group (SWOG) conducted a phase II trial (SWOG 9911) of CHOP chemotherapy followed by ^{131}I-Tositumomab consolidation for treatment-naïve advanced stage FL (Press, Unger et al. 2003). The overall RR was 90% (CR 67%, PR 23%). 27 of the 47 fully evaluable patients converted to CR following ^{131}I-Tositumomab consolidation. With a median follow-up of 2.3 years, the 2-year PFS was estimated to be 81%, and 2-year OS was 97%. 5-year follow-up of this trial (Press, Unger et al. 2006) reported PFS was 67% and OS was 87%. The overall RR was 91%, including a 69% CR rate. Compared to historical group of patients in SWOG database who were treated with CHOP, the estimated 5-year OS and PFS were 23% better. Molecular remission was seen in 7 patients (18%) after CHOP and 24 additional patients (63%) after tositumomab/iodine I-131 tositumomab therapy (Press, Unger et al. 2006).

Multiple other trials have compared RIT to fludarabine (Leonard, Coleman et al. 2005), CVP (Link, Martin et al.) or R-CHOP (Zinzani, Rossi et al. ; 2006) in first line treatment with excellent responses with CR between 60%-90%. Though, these treatments are very effective, they are still underutilized.

4.4 Newer-generation anti-CD20 antibodies

One of the newer generations of anti-CD20 antibodies is ofatumumab. This antibody is completely humanized IgG1 that recognized epitopes which are different than the ones recognized by R. Ofatumumab binds to a novel epitope of CD20, which encompass the small extracellular loop (residues 74 to 80) and the *N*-terminal region of the second large extracellular loop, including amino acid residues 163 and 166A (Teeling, Mackus et al. 2006). Coiffier et al published initial data on ofatumumab in patients with relapsed or refractory Chronic Lymphocytic leukemia (CLL) with RR of 50% and PFS of 106 days (Coiffier, Lepretre et al. 2008).

Ofatumumab as a single agent was studied in patients with CLL refractory to fludarabine and alemtuzumab (FA-ref) or refractory to fludarabine with bulky (> 5 cm) lymphadenopathy (BF-ref) (William Wierda 2009). FA-ref patients had overall RR of 58%, median PFS of 5.7 months, and median OS of 13.7 months. BF-ref patients had RR 47%,

median PFS of 5.9 months and median OS of 15.4 months. Subgroup analysis continued to show response irrespective of prior anti-CD20 monoclonal antibody therapy with R, including refractoriness to fludarabine-based regimens containing R (William Wierda 2009). Ofatumumab was also proven effective in patients with treatment-naïve CLL with RR of 72% and CR of 50% (William G Wierda 2009).

Currently in development are : ocrelizumab, a 2H7 murine monoclonal antibody (Kausar, Mustafa et al. 2009); veltuzumab (Immu-106, hA20) also seeks target 2H7 (Morschhauser, Leonard et al. 2009); obinutuzumab (GA101) which recognizes a different epitope (Niederfellner, Lammens et al.)

4.5 Alemtuzumab

Alemtuzumab (Campath®/MabCampath®; Bayer Schering Pharma, Berlin) is a fully humanized IgG1-type monoclonal antibody directed against CD52, a glycosylphosphatidylinositol-anchored cell surface glycoprotein expressed on human B and T cells, natural killer cells, eosinophils and macrophages (Treumann, Lifely et al. 1995).

Initial pilot study by Osterborg et al confirmed activity as well as safely of alemtuzumab in patients with CLL (Osterborg, Fassas et al. 1996). A larger phase II study showed RR of 87% with 19% CR in 41 newly diagnosed patients with CLL(Lundin, Kimby et al. 2002). In recent update median TTF was determined at 28 months (range 4 to 102+ months) (Karlsson, Norin et al. 2006).

A large phase III study (CAM307) randomized patients with newly diagnosed CLL to receive either alemtuzumab (30 mg iv tiw for 12 weeks) or chlorambucil (40 mg/m2 orally once every 28 days for up to 12 cycles) (Hillmen, Skotnicki et al. 2007). Alemtuzumab arm had significantly improved ORR (83%, Cr 24%) compared to chlorambucil arm (55%, CR 2%) (p<0.0001). Median time to alternate therapy was also significantly prolonged with alemtuzumab (23.3 months vs 14.7 months, HR 0.54, p<0.0001) (Hillmen, Skotnicki et al. 2007). This trial proved efficacy of alemtuzumab over purine analogues in treatment-naïve B cell CLL, and has been approved by FDA as a first line therapy.

T cells have high expression of surface CD52 antigen, highest being in T-prolymphocytic leukemia (T-PLL) (Ginaldi, De Martinis et al. 1998). A phase II open label study treated 27 treatment-naïve Peripheral T-cell Lymphoma (PTCL) patients with CHOP in combination with alemtuzumab (CHOP-C) for 8 cycles (Gallamini, Zaja et al. 2007). CR was achieved in 17 (71%) patients. At a median follow-up of 16 months, 13 patients were disease free, with median duration of response of 11 months (Gallamini, Zaja et al. 2007).

4.6 CD30

Hodgkin's lymphoma (HL) and anaplastic large-cell lymphoma are the two most common tumors expressing CD30. Brentuximab vedotin (SGN-35) is a monoclonal antibody that delivers monomethyl auristatin E to HL cells and utilized an anti-CD30 antibody to induce cell death, improved overall RR in patients with relapsed/refractory HL who has previously undergone ASCT.

Initial phase I trial reported excellent overall RR and tumor regression (Younes, Bartlett et al 2010). This led to larger pivotal phase II single arm study in patients with relapsed or refractory HL post ASCT (Chen R et.al)(Robert Chen 2010). Overall RR was 75% (34% CR, 40% PR) with tumor regression in 94% patients. Estimated 12-month OS was 88%. Currently a larger phase 3 study is ongoing to evaluate role of Brentuximab Vedotin (SGN-35) in patients at high risk of residual HL following ASCT (The AETHERA Trial) (NCT01100502).

Side effects:

The "targets" on the cancer drugs are often present in normal tissues to which leads to side effects. Due to limited space, the side effects experienced commonly by the most frequently use targeted agents are presented in the following table.

Target	Drug	Side effect
BCR-ABL	Imatinib	Nausea/vomiting, fluid retention with pleural effusions, ascites, pulmonary edema and weight gain, diarrhea, myelosupression (neutropenia and thrombocytopenia), skin toxicity
Immunomodulatory drugs	Thalidomide	Teratogenic toxicity, constipation, peripheral neuropathy, skin rash, day time sedation with larger doses, increased risk of thromboembolic events
	Lenalidomide	Teratogenic toxicity, myelosupression (neutropenia, thrombocytopenia that is usually reversible), increased risk of thromboembolic events, diarrhea or constipation
Proteosome Inhibitor	Bortezomib	Fatigue, malise, weakness, nausea/vomiting, diarrhea, myelosupression (neutropenia and thrombocytopenia that is usually reversible), peripheral sensory neuropathy, orthostatic hypotension, fever
Histone deacetylase (HDAC) inhibitor	Vorinostat	Nausea/vomiting, diarrhea, myelosupression (anemia and thrombocytopenia), fatigue, cardiac toxicity (QTc prolongation), hyperglycemia, increased risk of thromboembolic events
mTOR inhibitor	Temsirolimus	Fatigue, pruritus and pustular, acneiform skin rash, mucositis, hyperlipidemia, hyperglycemia, rarely bowel perforation, interstitial lung disease, renal toxicity, peripheral edema
CD20 receptor	Rituximab	Infusion related toxicities including anaphylaxis, tumor lysis syndrome, skin reaction ranging from pemphigus to toxic epidermal necrolysis, lymphopenia, rhinitis and dyspnea
CD52 receptor	Alemtuzumab	Infusion related reactions, increased incidence of opportunistic infections including Pneumocystis jiroveci, cytomegalovirus, herpes zoster, candida, Cryptococcus, myelosupression (neutropenia, rarely pancytopenia with marrow hypoplasia)

Table 4. Side effects of targeted treatment

5. Conclusion

Targeted therapies have changed the era of cancer treatment and their development is rapidly making headway. As listed above many are becoming front line therapies in combination with chemotherapy. Imatinib and ATRA have dramatically changed the course

of treatment for patients with CML or APL respectively. In addition, rituximab has improved RR and OS in patients with B-Cell lymphoma. Many other such drugs have been listed above and more drugs are in development. It is very crucial to understand the pathways and ''find the right target'' in specific diseases. This new knowledge about ''targets'' will hopefully help us choose personalized treatments for our patients one day, improving their survival with minimal impact on their quality of life.

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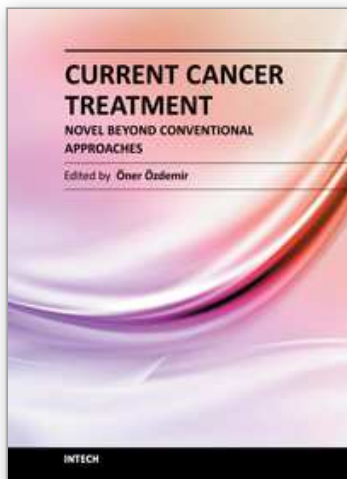
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Currently there have been many armamentaria to be used in cancer treatment. This indeed indicates that the final treatment has not yet been found. It seems this will take a long period of time to achieve. Thus, cancer treatment in general still seems to need new and more effective approaches. The book "Current Cancer Treatment - Novel Beyond Conventional Approaches", consisting of 33 chapters, will help get us physicians as well as patients enlightened with new research and developments in this area. This book is a valuable contribution to this area mentioning various modalities in cancer treatment such as some rare classic treatment approaches: treatment of metastatic liver disease of colorectal origin, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer; new therapeutic approaches of old techniques: laser-driven radiation therapy, laser photo-chemotherapy, new approaches targeting androgen receptor and many more emerging techniques.

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