Chapter

Drugs and Drug Candidates for the Treatment of Lymphoma

Kubra Acikalin Coskun, Merve Tutar, Elif Cansu Abay, Nazlican Yurekli, Mervenur Al and Yusuf Tutar

Abstract

Cancer is the biggest health problem worldwide due to its high mortality rate. Lymphoma is defined as a group of malignant diseases that is caused by clonal proliferation of lymphocytes and is classified under two major groups: Hodgkin lymphoma and non-Hodgkin lymphoma. Genetic predisposition and some environmental factors constitute risk factors. Symptoms of the disease include unexplained fever, swelling of lymph glands, swollen abdomen, tiredness, loss of appetite, frequent infections, and weight loss. Positron emission tomography (PET) and computed tomography (CT) scans, along with MRI, are widely used for the diagnosis of lymphoma. Advanced blood and lymph node biopsy tests are used to evaluate treatment effect on blood cells and to confirm the diagnosis of lymphoma, respectively. Current treatment options include chemotherapy, radiotherapy, and bone marrow/stem cell transplantation. Development of new treatment options for cancer medications includes small molecules and monoclonal antibodies for immunotherapy. In addition, the discovery of new phytochemical agents used in complementary and alternative medicine adds perspective to the treatment of lymphoma.

Keywords: lymphoma, small molecule inhibitor, alternative medicine, herbal treatment, cancer treatments

1. Introduction

Lymphoma is lymphoid system malignancy developed from lymphocytes of the immune system with diverse morphologic and distinct clinical findings. Three classes of lymphocytes are natural killer cells (NK), T cells, and B cells. They function in cytotoxic innate immunity, cytotoxic adaptive immunity, and humoral antibody-driven adaptive immunity, respectively. The lymphatic system (lymph, lymph nodes, lymphatic vessels, collecting ducts) is a network of tissues, vessels, and organs (spleen, thymus, tonsils and adenoid, bone marrow, Peyer's patches, appendix), and lymphoma can develop in these organs. However, lymphoma is classified into two classes: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphomas are more frequently seen, approximately 8 times more, than the others. Distinct lymphomas arise from immune system cells at different stages of differentiation. In addition, all groups are divided into different types within themselves. Each one of these have different clinical course, response to treatment, and drugs used in their treatment [1–3].

To treat lymphomas, different treatment approaches have been developed, including chemotherapies, radiotherapies, and bone marrow transplantation. Radiotherapies create extensive damage and leave permanent effects on cancer patients even they are effective in treatment of lymphomas. Further, bone marrow transplantation is a challenging way due to suppressed immunity and may lead rising of infectious diseases in the patients. However, in certain cases, immunotherapies (i.e. with rituximab antibody which binds cell surface protein CD20) can lead to complete responses in lymphomas with minimal side effects. Nevertheless, to benefit from the effect of metabolites from plants several studies are underway to find a better therapeutic approach [2].

1.1 Plants in the treatment of lymphoma

Several approaches in the treatment of these diseases resulted in successful outcomes and yet some have adverse effects. Plants ingredients constitute more than 90% of commercial medical drugs and different plants may be employed for treating distinct malignant diseases [3].

1.1.1 Quercetin

This agent has anti-malignant effects and it possesses a cytotoxic effect over transformed lymphoid cells by targeting key pathways such as PI3K and Wnt. Synergetic and/or additive effects of quercetin in combination with other drugs are underway to display its therapeutic effects in various lymphoma types [4].

1.1.2 Salvianolic acid from Salvia miltiorrhiza *extracts*

The phenolic salvianolic acid A display anti-tumoral activity. Diffuse B cell lymphoma treatment options are limited and the activity is used against diffuse B cell lymphoma cells. The salvianolic acid inhibited the viability of the cells by inducing apoptosis. The apoptotic pathway induces by upregulation of Bax and cleavage of PARP. *In vivo* xerograph models also displayed tumor growth suppression with salvianolic acid A and the agent showed promising anti-tumoral activity for diffuse large B cell lymphoma (DLBCL) [5].

1.1.3 Annona muricata *Linn leaf extracts*

The activity of the leaf extracts is attributed to the secondary metabolites (phenols, flavonoids, alkaloids, acetogenins). The extracts were tested against Dalton's Lymphoma Ascites (DLA) and Ehrlich Ascites Carcinoma (EAC) cells and anti-tumoral effects compared to cisplatin. Cytotoxic studies indicated poor outcomes at lower microgram concentration per milliliter but tumor burden is decreased in dose-dependent manner and tumor volume is reduced significantly with a prolonged lifespan [6].

1.1.4 Amomum subulatum

Methanolic extracts of *Amomum subulatum* dry fruits administration induces apoptosis on Dalton's Lymphoma Ascites cells both *in vitro* and *in vivo*. The extracts further increase mouse life span through regulation of pro-inflammatory cytokines and NF-κB pathway by promoting apoptosis of cancer cells. The research employed cyclophosphamide drug as positive control and the extracts displayed better activity compared to the drug. Therefore, the study proposed *A. subulatum* as a potential nutraceutical (nutrition-based therapeutic) against cancer [7].

1.1.5 Gymnopilus purpureosquamulosus *extracts*

The extract activates apoptosis indicated by annexin V-positive cells and further, production of reactive oxygen species, PARP1 cleavage, and mitochondrial membrane potential decrease upon extract treatment. The extract also displayed apoptosis in lymphoma patient cells but not in healthy patient cells [8].

1.1.6 Ingenol mebutate extract

A new therapeutic agent from *ingenol mebutate extract* displayed apoptotic activity against cutaneous T-cell lymphoma. The agent activated caspase by downregulating c-FLIP and XIAP and can be employed as a potential drug candidate [9].

1.1.7 Cucurbitacin B

Primary effusion lymphoma (PEL) is an aggressive B cell non-Hodgkin lymphoma that has been seen in immunocompromised patients. Cucurbitaceae B is a triterpene extracted from *Cucurbitaceae* plant that has several anti-cancer activities. The effect of Cucurbitaceae B was examined at distinct PEL cell lines. The agent inhibited cell proliferation of PEL cell lines Further, a xenograft model was also employed and the agent suppressed solid tumor growth. The reports proposed that Cucurbitaceae B is a promising agent as an antitumoral activity for PEL [10].

1.1.8 Achyranthes aspera *L. leaf extract*

The extract was tested against Dalton's lymphoma (DL) both *in vitro* and *in vivo*. The extract suppresses DL through attenuation of the PKCα signaling pathway and mitochondrial apoptosis [11].

Therefore, several metabolites from plant extracts potentially display anti-tumoral activity and can be used both for nutraceutical and drug design for lymphoma treatment but further research is required to optimize these agents for drug development.

1.2 Small molecule inhibitors in lymphoma

Small molecule inhibitors are usually analogs of target protein substrates like ATP or phosphotyrosine. Due to their small size, these inhibitors effectively reach and interact with their targets that are extracellular receptors, cell surface ligand-binding receptors, and intracellular proteins which include anti-apoptotic proteins known for playing an important role in transducing downstream signaling for cell growth and metastasis progression. Anti-cancer small molecule inhibitors are therapeutic agents that target key proteins in pathways involved in cell proliferation and differentiation [12].

Small molecular inhibitors (SMIs) are able to target tumor cells due to the disturbed cellular architecture [13]. Disturbed architecture is an advantage for SMIs to diffuse in the gaps between the tumor cells and reach their targets [14]. With the help of this advantage, SMIs are promising approach for the treatment of multiple tumors. Therefore, researchers develop target-specific SMIs targeting critical malignant pathways. The combination of SMIs with clinical chemotherapy agents may increase treatment efficiency [15, 16].

In the case of lymphoma, similar to other cancer cells, many of the proteins associated with the survival, angiogenesis, and metastasis of cancer cells are hyperactivated. To suppress the hyperactivation, specific proteins in lymphoma are targeted namely Bruton tyrosine kinase, PI3K, HDACs, and proteasomal system proteins [17].

1.3 FDA approved and non-approved small molecule drugs in treatment of lymphoma

The number of drugs for the treatment of lymphoma has increased with the findings of new agents. Regulatory agencies have approved many novel drugs for the treatment of various forms of lymphoid malignancies over the last two decades. Several drugs for the treatment of lymphoma include the B-cell receptor signaling inhibitor ibrutinib, the antibody-drug conjugate brentuximab vedotin, the PI3K-δ inhibitor idelalisib, the novel glycoengineered anti-CD20 antibody obinutuzumab, and the immunomodulatory drug lenalidomide [18].

The majority of novel treatments for NHL were approved for follicular B cell lymphoma. On the other hand, there are only two drugs for relapsed diffuse large B cell lymphoma in the past three decades. In some cases, a unique molecular mechanism is targeted by approved drugs while in others, multiple agents targeted the same oncogenic pathway, including the PI3 kinase pathway and Bruton tyrosine kinase (BTK). Furthermore, there are many investigational agents that target the intracellular mechanisms have studied [19].

Several antibody-drug conjugates and the BCL2 inhibitor venetoclax are some examples of unapproved targeted drugs that have shown promising efficacy. Additionally, various immunotherapies, such as mono- and bispecific antibodies, immune-checkpoint inhibitors, and engineered chimeric antigen receptor (CAR) T cells, have also shown efficacy in lymphoma patients [18]. Therefore, in view of the multitude of new agents, the finding of drugs for the treatment of lymphoma has grown, demanding the efficient prioritization of drugs for faster development. Here, additional focus will be given to overview of the U.S. Food and Drug Administration (FDA) approved drugs for the treatment of lymphoma and drug development at new targets.

1.3.1 Bruton tyrosine kinase (BTK) inhibitors

BTK is an important therapeutic target for B-cell NHL because it plays a crucial role in the BCR signaling pathway [20]. Ibrutinib is a BTK inhibitor, that binds to BTK's Cysteine 481 (C481) site in an irreversible manner, disrupting the antigen-dependent active BCR signaling pathway [21]. This inhibitor is approved by the FDA for the treatment of chronic lymphocytic leukemia (CLL), mantle-cell lymphoma (MCL), and Waldenstrom macroglobulinemia (WM) [22].

Ibrutinib resistance has been shown to be conferred by acquired mutations in the C481 binding site, as well as gain-of-function mutations in the downstream PLCγ2 kinase increasing BCR signaling [23]. In order to overcome ibrutinib resistance by inhibiting both wild-type and C481-mutated BTK non-covalently, novel highly selective BTK inhibitors are currently being investigated [24]. Ibrutinib was approved by the US FDA-approved for the treatment of WM demonstrating a 90.5% overall response rate (ORR) [25]. Ibrutinib is also FDA approved inhibitor for MCL after ≥1 prior line of therapy and for MZL after ≥1 prior anti-CD20-directed therapy [26, 27]. Because of its capacity to permeate the blood-brain barrier, ibrutinib has shown a promising effect on primary central nervous system (CNS) lymphoma [28]. Combining therapies, ibrutinib with venetoclax, lenalidomide, second-generation anti-CD20 mAbs, immune checkpoint inhibitors, and chimeric antigen receptor (CAR) T-cell therapy are still investigating in different NHLs [22].

Acalabrutinib is another BTK inhibitor and when it is compared to ibrutinib, it has less off-target kinase inhibition and a better safety profile. Patients with severe liver disease, as well as those using powerful CYP3A inhibitors and inducers or proton pump inhibitors, should avoid acalabrutinib. According to a phase II trial

that demonstrates 81% ORR, acalabrutinib was approved by FDA for MCL [29]. In addition, zanubrutinib is FDA BTK inhibitor for MCL ≥1 prior line of therapy. Patients with severe liver disease or who are taking CYP3A inhibitors and inducers at the same time should alter their doses [30].

1.3.2 Immunomodulatory drugs (IMiDs)

Immunomodulators (IMiDs) bind cereblon E3 ubiquitin ligase complex that degrades the transcription factors of Aiolos and Ikraos. In this way, it results in the direct death of malignant B cells as well as overexpression of IL-2, which leads to T and NK cell activation [31]. Teratogenicity, cytopenias, infection, thrombosis, secondary malignancy, and rash are all side effects of the IMiD class [32].

Lenalidomide is a second-generation IMiD that is given at a daily dose of 20–25 mg for the first 21 days of a 28-day therapy cycle. Despite, lenalidomide's single-agent ORR for relapsed indolent lymphoma is low (23%), this drug is still used in combination with rituximab (R) (anti-CD20 monoclonal antibody (mAb)) for relapsed/refractory follicular lymphoma (FL) and marginal zone lymphoma (MZL) treatment. In addition, lenalidomide has shown activity in patients with relapsed/refractory MCL with an ORR of 28%. In a randomized phase II trial, relapsed MCL patients who got single-agent lenalidomide had a better ORR than those who received other single agents (40% vs. 11%). Lenalidomide was approved by the FDA in the United States for relapsed/refractory MCL after ≥2 prior therapies, including bortezomib [22].

1.3.3 Phosphoinositide 3-kinase (PI3K) inhibitors

PI3K activates AKT and mTOR via the B-cell receptor signaling pathway, resulting in enhanced cell survival. Class 1 PI3K has four distinct isoforms: α, β, γ, and δ with significantly expressed in lymphocytes. In NHL, inhibiting this pathway with PI3K inhibitors is a key focus [22].

Idelalisib is a PI3K inhibitor that targets PI3K specifically, and it has been approved by FDA as a single-agent treatment for patients with relapsed/refractory FL [33]. Copanlisib is the other US FDA inhibitor that targets α and δ isoforms for relapsed FL. In addition, it has specificity for the α isoform that has a role in insulin and glucose metabolism. For this reason, unique toxicity of hyperglycemia, liver toxicity, diarrhea, neutropenia, and infection are observed [34]. Lastly, duvelisib is a dual PI3K FDA approval inhibitor for relapsed/refractory FL after ≥2 prior systemic therapies. Inhibition of both the γ and the δ isoforms is expected to be synergistic since it targets both B cell proliferation and survival as well as the tumor microenvironment. In a phase II clinical trial, duvelisib was tested as a single treatment in indolent NHL and exhibited an ORR of 47.3% [35].

1.3.4 Proteasome inhibitors

Proteasome inhibitors prevent ubiquitin-tagged proteins from being degraded, affecting cellular homeostasis and triggering apoptosis. Bortezomib is a proteasome inhibitor and it was approved by the FDA in the United States for the treatment of MCL based on a phase II study with an ORR of 33% [36]. Additionally, bortezomib also received U.S. FDA approval in combination with R-cyclophosphamide, doxorubicin, prednisone (R-CAP) for untreated MCL [37]. Plasmablastic lymphoma, Waldenstrom's macroglobulinemia (WM), and peripheral T cell lymphomas (PTCL) had promising activity by bortezomib [38, 39] while randomized trials showed no benefit from adding it to frontline chemoimmunotherapy for DLBCL and FL [40].

1.3.5 Histone deacetylase inhibitors

Histone deacetylase (HDAC) inhibitors work against cancer by altering the acetylation of histone and transcription factor proteins, causing cell cycle arrest and apoptosis. The inhibitor romidepsin was approved by FDA for the treatment of relapsed/refractory PTCL demonstrating ORR 25–38% in phase II studies [41]. Moreover, romidepsin is being tested for relapsed/refractory NHLs in combination with lenalidomide, the folate antagonist pralatrexate, and the immune checkpoint inhibitor pembrolizumab [22].

The other FDA-approved HDAC inhibitor is belinostat for the treatment of relapsed/refractory PTCL demonstrating a 26% ORR [42]. Vorinostat is also FDA approved HDAC inhibitor after two prior lines of systemic therapies for cutaneous T cell lymphomas (CTCL) that have progressed with a 30% ORR [43].

1.3.6 Selective nuclear export inhibitors (SINE)

Selinexor, a selective inhibitor of nuclear export (SINE) prevents tumor suppressor genes from being exported from the nucleus by inhibiting the shuttling protein exportin 1 (XPO1) [22]. Cytopenias, anorexia, nausea, vomiting, diarrhea, tiredness, hyponatremia, infections, and neurological toxicity are the most prevalent significant side effects of selinexor [33]. Selinexor is approved by U.S. FDA for the treatment of relapsed/refractory DLBCL. Moreover, it is being studied in combination with standard R-CHOP chemoimmunotherapy for the initial treatment of DLBCL, as well as in combination with venetoclax or salvage chemoimmunotherapy [22].

1.3.7 EZH2 (enhancer of zeste homolog 2) inhibitors

EZH2 is a histone-lysine N-methyltransferase enzyme; a histone methyltransferase responsible for methylation of lysine 27 of histone H3 (H3Lys27). In addition, a DNA alteration is linked to repressed transcription when it is trimethylated (H3Lys27me3). That is why, abnormal EZH2 activity that activates mutations, has been identified as an oncogenic driver [18].

In 22–29% of patients with FL, mutations in the EZH2 gene have been observed. A phase II study revealed that tazemetostat had an ORR of 69% in EZH2-mutated FL and 35% in EZH2 wild-type FL in 99 patients with relapsed/refractory FL. According to these results, tazemetostat was approved by U.S. FDA for patients with EZH2-mutated FL. Furthermore, the effect of tazemetostat in relapsed/refractory B-cell lymphomas is being investigated in a variety of early-phase studies [23].

1.4 Lymphoma drug candidates

Different approaches have been developed and applied to cure lymphoma [19]. There are few drugs approved by FDA. However, efficient therapeutics to treat lymphomas are still under investigation. Researchers have been working on novel agents. Recent studies have discovered promising drug candidates for lymphoma cancer cells [44]. Researchers have still been working on few drug candidates [45]. These candidates can be classified according to their target signaling pathways as follows:

1.4.1 SYK inhibitors

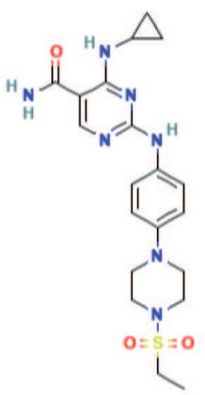
Cerdulatinib is an inhibitor of SYK, JAK1, JAK3, and TYK2 and was investigated in phase 1 experiments. Preclinical and clinical research showed that cerdulatinib

inhibits SYK/JAK signaling cascade activity and showed promising effects on diffuse large B cell lymphoma. In a research report, a phase 1 dose study of cerdulatinib drug in 43 patients with r/r CLL and NHL was completed in 2016 and according to results, SYK and JAK inhibition was well tolerated and antitumor activity of the drug was proved in CLL and FL patients [45].

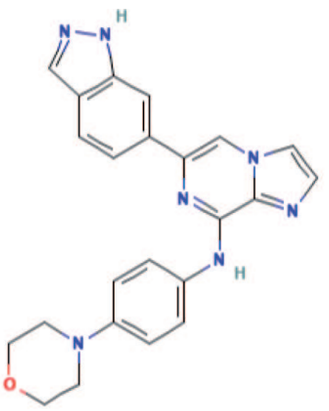
Entospletinib is a small-molecule inhibitor that specifically binds and inhibits the SYK activity. Phase 2 studies showed that usage of the inhibitor with other drugs as a combined therapy resulted in inhibition of BCL signaling activity [46].

Fostamatinib: Phase 1/2 clinical trial of fostamatinib disodium drug which is classified as the first clinically available oral SYK inhibitor was applied in patients with recurrent B-cell non-Hodgkin lymphoma (B-NHL). Results showed that the drug has ability to induce apoptosis by inhibition of SYK [47].

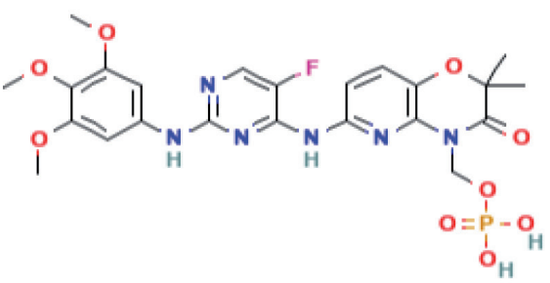
Mivavotinib TAK659: Last drug that inhibits SYK activity to block BCL signaling pathway and results in inhibition of activation, adhesion, and proliferation of B-cell. Phase 1 study is completed, however, phase 2 study was not completed due to the lack of step 1 in the designed experiments [48].



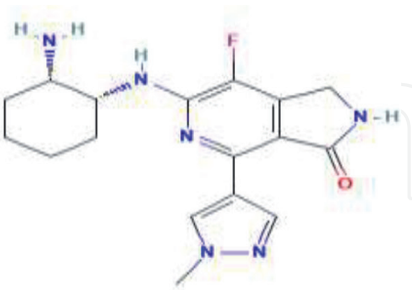
Cerdulatinib (PubChem CID: 44595079)



Entospletinib (PubChem CID: 59473233)



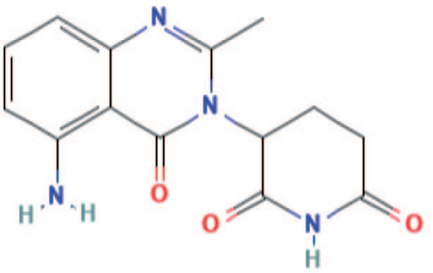
Fostamatinib (PubChem CID: 11671467)



Mivavotinib TAK659(PubChem CID:53252276)

1.4.2 IMID inhibitors

Avadomide CC-122 is cereblon-modulating agent that has a potential antineoplastic, antiangiogenic and immunomodulatory activity in the cell. Avadomide has a role in the ubiquitination and rapid proteasomal degradation of Aiolos and Ikaros proteins which are the hematopoietic transcriptional factors and induce apoptosis of DLBCL. Treatment including avadomide with another anti-lymphoma drugs combination is suggested for the best results [49].



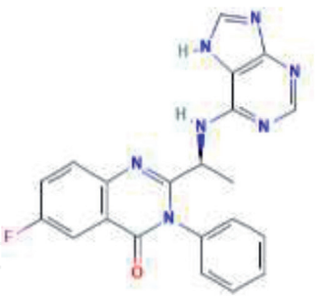
Avadomide CC-122(PubChem CID:24967599)

1.4.3 PI3K/PI3Kδ-pan PI3K inhibitors

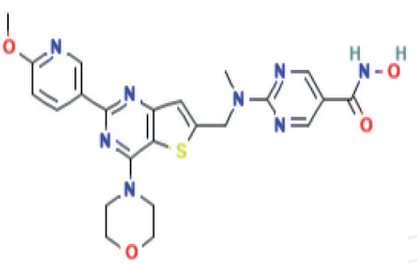
Acalisib (GS-9820, 6-fluoro-3-phenyl-2-[(1S)-1-(9Hpurin-6-ylamino) ethyl]-4(3H)-quinazolinone): acalisib is a drug candidate for all lymphoma types including CLL, NHL. Phase 1 research showed in a human basophil activation experiment that Acalisib molecule suppresses IgE receptor by PI3Kδ-mediated CD63 expression [50].

Fimepinostat CUDC-907: a small molecule inhibits HDAC/PI3K. According to the researchers, at phase 1 experiments, dual HDAC/PI3K inhibition with fimepinostat CUDC-907 showed a well-tolerated activity in suppression of target protein activities and further, low toxicity profile was observed [48].

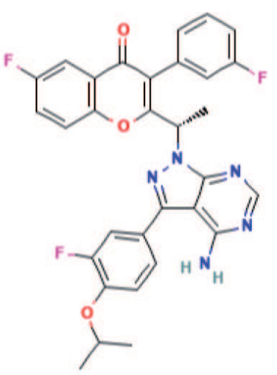
Umbralisib is an oral inhibitor of PI3K-delta and CK1-epsilon. Cellular functions of the PI3K-delta include cell proliferation and survival, cell differentiation, intracellular trafficking, and immunity. CK1-epsilon regulates oncoprotein regulation and the process drives the growth and survival of lymphoma. The inhibitor is in phase 2b and phase 3 trials in NHL and CLL patients. In the phase 1 study, side effects are observed in the lymphoma patients including diarrhea, nausea, and fatigue [51].



Acalisib (GS-9820) (PubChem CID:11618268)



Fimepinostat CUDC-907 (PubChem CID:54575456)

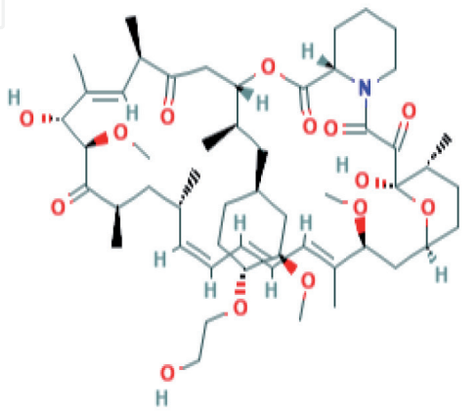


Umbralisib (PubChem CID:72950888)

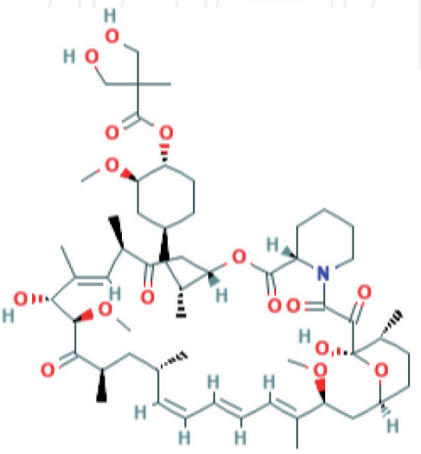
1.4.4 mTOR inhibitors

Everolimus is an oral mTOR inhibitor and is used against relapsed lymphomas. A recent phase 2 study have shown that everolimus dramatically increases the efficiency of treatment in lymphoma patients when it is combined with other anti-lymphoma drugs [52].

Temsirolimus is an mTOR inhibitor that inhibits the synthesis of the proteins such as VEGF (vascular endothelial growth factor) that have role in cell proliferation and survival in mantle-cell lymphoma [53].



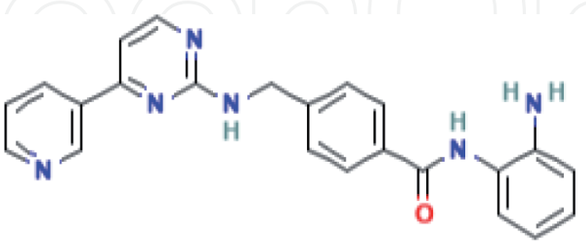
Everolimus (PubChem CID: 6442177)



Temsirolimus (PubChem CID: 6918289)

1.4.5 HDAC (histone deacetylase) inhibitors

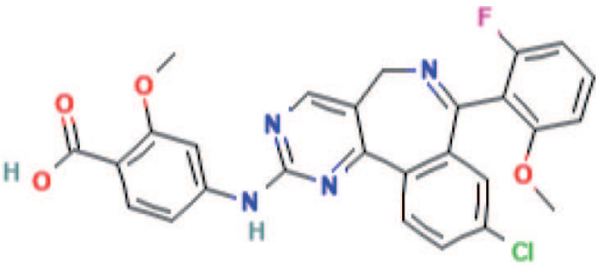
Mocetinostat MGCD0103 is classified as a HDAC inhibitor. Phase 2 study showed that a combination of mocetinostat with other anti-lymphoma agents resulted in higher efficiency in the treatment of lymphomas compared to the application of mocetinostat alone [54].



Mocetinostat MGCD0103 (PubChem CID: 9865515)

1.4.6 Aurora A kinase inhibitors

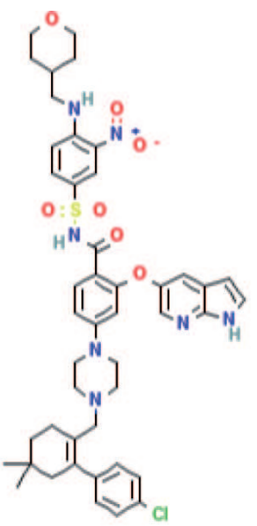
Alisertib is an Aurora A kinase inhibitor. This inhibitor leads to abnormal mitotic spindle formation that causes mitotic cell accumulation and lowers tumor cell proliferation upon treatment of malignant cells. Since Aurora A kinase has a mitotic role in the cancer cells, anti-mitotic agents may have benefits to treat lymphoma [55, 56].



Alisertib (PubChem CID: 24771867)

1.4.7 BCL2 inhibitors

Venetoclax is a BLC2 inhibitor and BCL2 is highly expressed at CLL. The protein helps CLL cancer cells to survive and provide resistance to drugs. Venotoclax binds CLL to slow down the progression. Treatment of venetoclax with the other anti-lymphoma agents like ibrutinib displayed higher drug efficiency in patients at phase 2 trials. In the light of phase 2 results, researchers combine venetoclax with anti-lymphoma agents in phase 3 trials [57]. Combination drug treatment of venetoclax with obinutuzumab is FDA approved treatment and currently used against lymphomas [58].



Venetoclax (PubChem CID: 49846579)

2. Conclusion

Cancer with all of its different types is a big health issue for everyone around the world. Lymphoma is one of the most common types of cancer [1]. Like all other cancer types, it has its own risk factors, causes, and treatments that are still open to discovery. Besides other cancer types, lymphoma is defined as cancer transformation of lymphoid cells. Hodgkin lymphoma and non-Hodgkin lymphoma are the main subtypes of lymphoma [1].

The treatment options for lymphoma include chemotherapy, radiotherapy, and bone marrow transplantation but research to develop the treatment options are still underway. As mentioned above, small molecule inhibitor agents are new perspectives found for the traditional treatment options for lymphoma.

The drugs and potential anticancer agents for lymphoma are mentioned in detail in this review.

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