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Chapter

Target Therapy in Hematological Malignancies

Safa Shukry, Fadhel Hariri and Abdul Wahab Al-Nehmi

Abstract

Molecular target therapy is a recently rapid progress in the management of hematological malignancies. In myeloid neoplasm, the sensational response to treatment and the overall survival and quality of life improvement for treatment with tyrosine kinase inhibitors (TKI) agents for patients with chronic myeloid leukemia and the introduction of Janus kinase (JAK)-2 inhibitors (ruxolitinib) may offer comparative advantage in myeloproliferative diseases of patients with polycythemia vera (PV), primary myelofibrosis (MF) and essential thrombocytosis (ET). The introduction of all-trans-retinoic acid (ATRA) and mylotarg for acute myeloid leukemia patients, have had major impacts on the treatment protocol plan and different other targeted therapeutic highly effective agents, including FLT3, histone deacetylase inhibitors and farnesyl transferase. In malignant lymphomas and lymphatic leukemia the feature has been the presentation of rituximab, with critical enhancements within the treatment of chronic lymphocytic leukemia and non-Hodgkin’s lymphoma. The most recent 15 years has encountered a rapidly broadening interest and acknowledgment that leukemic stem cells, including an enhanced capacity to target them, may hold the way to enhanced reaction and diminished relapse rates over both lymphoid and myeloid disorders. Technical regulation for growing new personalized anticancer target therapy agents have changed and presently evaluated and screened.

Keywords: target therapy, hematological malignancy, leukemia, lymphoma, myeloma

1. Introduction

The past few a long time have seen gigantic changes within inside the approach to making advanced anticancer therapy, in one side due to advanced unused innovations and computer instruments, and on other side due to other ways of inquire about centered on progressing our understanding about the fundamental of molecular pathways and genetic changes that driving the advancement of cancer, discoveries which are making a difference us to superior distinguish which patients will advantage from the plan focused on treatment and permit the researcher to personalized target therapy guidelines. This ever-growing information base has too driven to the distinguishing proof of more molecular targets and the ensuing development of new focused on target therapy agents that will shaping treatment of cancer in the future [1].
Personalized targeted therapy is a drug that squares the cancer cells development by interfering with particular molecule needed for carcinogenesis and growth of tumors [2] instead of essentially interfering with quickly isolating dividing cells. The personalized targeted therapy for cancer diseases has been a noteworthy stimulus for the advancing field of pharmacogenomics. Moreover it is characterized as pharmacogenomics can envelop germline and significant (infection) gene and protein estimations utilized to expect the probability that a patient's tumor will react to an explicit single-agent or multiagent chemotherapy protocols and the chance of hurtful side effects [3]. Besides the US Food and Drug Administration (FDA) has considered target treatment as a personalized therapy approved and named with a specific reference to at the same time or as of now asserted illustrative test that must be performed some time recently the persistent can be considered qualified to get the target therapy agents [4].

Personalized targeted therapy begun modern transformation approximately the improvement of cancer treatment to a person patient's tumor, the financial matters of cancer care around the world. As expanded of analyzed patients with cancer and as these patients live longer, essential care clinics will make strides wellbeing care for patients who have gotten cancer target therapy [5, 6].

2. Development of target therapy

The outcome after revolution of target therapy was improved in lymphoma, myeloma and chronic leukemia. Imatinib as first generation of TKI has had an excellent outcome on chronic myeloid leukemia, bortezomib and rituximab, which has also high percentage of remission in myeloma and lymphoma, respectively [7, 8]. In patients with multiple myeloma preclinical studies have informed the rational use of combination therapies, such as bortezomib with lenalidomide to trigger both intrinsic and extrinsic apoptotic signaling [9].

Chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL) and idiopathic myelofibrosis (IM) fundamentally influence elderly patients, numerous of whom have therapeutic comorbidities that constrain the utilize of standard chemotherapy. Treatment with target therapy such as imatinib and rituximab are frequently less harmful and superior endured than conventional chemotherapy, advertising these patients extra treatment choices [10].

3. Acute myeloid leukemia (AML)

The targeted therapy for patients with AML in recent years maybe most outstanding within the molecularly targeted therapy against its specific genetic abnormality of acute promyelocytic leukemia (APL). The initial (induction) treatment of APL with all-trans-retinoic acid (ATRA) play role in cells differentiation in patients with APL with t(15;17) (q22;q21) and has driven to disease-free survival and/or cure in 75% of patients with APL [11].

The introduction of ATRA in patients works to differentiation blast of acute promyelocytic leukemia (APL) to AML blast. The retinoic acid disorder is the most common complication characterized by fever, disseminated intravascular coagulation and cardiac, respiratory and renal function disorders. These disorders, which are seen in some patients, particularly patients associated with leukocytosis, can be treated or improved with chemotherapy or corticosteroids.

The current standard treatment of APL in induction and consolidation, include introduction of ATRA simultaneously with cytarabine and anthracycline and pursued by maintenance in combination with low-dose chemotherapy [12, 13].
Moreover, in an endeavor to maintain a strategic distance from routine chemotherapy, the addition of ATRA in combination with gemtuzumab ozogamicin has been utilized as induction with achievement of remissions (Table 1) [14]. Gemtuzumab ozogamicin (GO; Mylotarg) is a selective anti CD33 anti-body conjugated with calicheamicin facilitated against CD33 surface marker and communicated by more than 90% of myeloid leukemic blasts and is harmful to DNA calicheamicin. The overall response (OR) rate reported in 30% patients with AML and CD33+ treated with GO.

The rate of myelosuppression as common side effects of chemotherapy, was less with GO, in spite of the fact that acute respiratory distress syndrome and pulmonary edema have been experienced in patients with leukocytosis but less than 30,000/mL [15]. In May 2000, FDA have approved “GO” for patients above 60 years and after relapsing or for patients not fit for intensive chemotherapy [15–19]. On September 1, 2017, the (FDA) also approved “GO” for adult patients newly diagnosed AML with CD33+.

Ulocuplumab (BMS-936564/MDX-1338) may be a monoclonal antibodies agent which inhibits the official of the CXC chemokine receptor 4 (CXCR4) to fortify relocation from the bone marrow to peripheral blood stromal cell-derived chemokine CXC theme ligand 12 (CXCL12). In patients with refractory and relapsed AML, ulocuplumab in combination with mitoxantrone, etoposide and cytarabine driven to CR with partial recovery of bone marrow cell lines (CRi) in 51% patients studied [20].

The mutations of FLT 3 appear to be free destitute prognosticators in AML. The Mutation in FLT3 gene (FMS-like tyrosine kinase-3) occurs in 30% of FLT3-ITD and 7% of FLT3-TDK with AML. The FLT3 kinase inhibitors may be divided into 1st- and 2nd-generation drugs. 1st-generation: sorafenib, sunitinib, estaurtinib, midostaurin I, tandutinib, pacritinib; 2nd-generation: gliteritinib, quizartinib, crenolamid, ponatinib, JH-IX-179, PLX3397. The mutated FLT3 gene has variable affectability according to type of target therapy [21].

Isocitrate dehydrogenase (IDH) takes place in lipid metabolism and the Krebs cycle, and it catalyzes the change of isocitrate to α-ketoglutarate. In AML the gene mutations IDH1 occur in 11% and IDH2 in 12% of cases. Enasidenib (AG-221/ CC-90007) is the first single-agent selective IDH2 inhibitor to induce the differentiation of leukemic cells and orally well tolerated. AML in patients with refractory or relapsed with mutant-IDH2 induced hematologic responses, and have more than 9 months median survival reported after treatment with Enasidenib [22].

### Table 1.
Targeted drugs in AML treatment.
Navitoclax is BCL2 inhibitor by ABT-199 with multiple anti-apoptotic of AML. Its antitumor activity is restricted by adverse effects, which is registered by the FDA for treating chronic lymphocytic leukemia (CLL) and AML [23]. Vosaroxin could be a topoisomerase II inhibitor which is one of the important randomized trials exploring therapeutic options for refractory and relapsed AML to date and considered basic for cell survival. Vosaroxin induces DNA destruction and is most successful among elderly patients more than 60 years of age with myelodysplastic disorder (MDS) or acute myeloid leukemia (AML) [24]. Lysine-specific demethylase 1 (LSD1) is a histone demethylase. LSD1 inhibition leads to the inhibition of growth and metastasis of tumor and also regulates the differentiation of stem cells and has potential novel treatment in acute myeloid leukemia (AML).

Panobinostat (LBH589) induces AML cell apoptosis in vitro by inhibiting the expression of repair proteins (e.g., BRCA1, CHK1 and RAD51), increasing the efficiency of cytarabine and daunorubicin, and it is promising in t(8;21) AML due to the pathological AML1/ETO protein that recruits histone deacetylases and in combination with Azacitidine (AZA) doubled the rate of response in high risk patients with CMML, MDS or AML not candidate for stem cell transplantation [25]. Vorinostat (suberoylanilidehydroxamic acid [SAHA]) advances cell cycle inhibition of growth and induces differentiation and cell apoptosis of AML and reported favorable overall survival in AML patients with FLT3 ITD mutations [26].

4. Acute lymphoblastic leukemia (ALL)

The classical main treatment for adult acute lymphoblastic leukemia (ALL) is chemotherapy drugs and in some patients the transplant of stem cells in adult patients has good results. Advance enhancement maybe calls for a diverse approach from conventional chemotherapy, such as target drugs with TKI (imatinib) and/or immunotherapy.

ALL with Philadelphia chromosome-positive (Ph+) have been noted with impressive response to intensive chemotherapy and imatinib [27]. CD20 is a B cell-specific surface antigen on mature B-ALL and precursor B-ALL, as well as in lymphoblastic lymphoma, would manage the probability of rituximab response. The introduction of target therapy (rituximab) in combination with chemotherapy (Hyper-CVAD) (rituximab with hyperfractionated cyclophosphamide, doxorubicin, vincristine and dexamethasone) in lymphoma or leukemia, reported complete remission rate of 90% with minimal toxicity [28, 29]. Acute lymphoblastic leukemia blast cells express specific antigens for CD22 in 90% of patients and have amazing clinical action indeed among intensely before treatment of elderly B-ALL patients and refractory and relapsed B-ALL patients after treatment with inotuzumab ozogamicin. Combination of inotuzumab ozogamicin with other treatments after chemotherapy may too possibly improve clinical outcomes [30].

Blinatumomab: is a CD3 and CD19-directed, to activate a B-cell specific inflammatory and cytolytic response. In 2006 FDA approved Blinatumomab for refractory and relapsed ALL [31]. Blinatumomab activates endogenous T cells by connecting CD19 on benign and malignant B cells with CD3 in the T-cell receptor complex in combination with chemotherapy or as single agents, in preclinical and clinical settings have produced varying response to induce tumor cell lysis via complement-dependent cytotoxicity or with antibody, induce cell death [32, 33].
5. Chronic myeloid (Myelogenous) leukemia (CML)

Chronic Myelogenous Leukemia (CML) is a clonal myeloproliferative disorder characterized by the increased and unregulated growth of myeloid cells due to translocation between long arms of chromosomes 9 and 22t (9;22) that generates tyrosine kinase BCR-ABL1 [34]. CML classified into 3 phases; chronic stable phase (CP) which the myeloid cell series is expanded but cellular differentiation is maintained and effortlessly controlled with treatment for a period that can last for 36–60 months but the accelerated phase (AP) can lasts for less than 12 months. Blast phase (BP) are still poorly understood, characterized by rapid expansion of myeloid or lymphoid with presence of more than 20% blast cells in the peripheral blood or bone marrow resulting in manifestation of ALL or AML and death in short period within 4–6 months [35].

Chronic myeloid (Myelogenous) leukemia treatment progressed significantly through the advancement of tyrosine kinase inhibitors (TKIs), particularly the presentation of imatinib into the clinical use. Imatinib is the drug of choice of the first generation in the chronic phase of CML and considered the golden standard target therapy in CML. The second generations also currently available for clinical use include nilotinib, dasatinib, bosutinib and ponatinib.

To maintain patients in remission and prevent progression of disease into accelerated and blast phases are the main treatment goals of chronic myeloid leukemias and keep the patients free of complications and with minimal drug related toxicity.

Target therapy with TKIs and allogenic bone marrow transplantation, play important role in improvement curative percentage of CML patients.

5.1 Imatinib (Gleevec)

Imatinib mesylate (IM), a phenylaminopyrimidine TKI that is the first drug of its class characterized by BCR-ABL TKI has excellent changes in the strategy of treatment of CML in the last 20 years. In May 2001, FDA has approved imatinib for the treatment of CML patients. Arthralgia, myalgia, nausea, and fluid retention are the common side effects in imatinib. About 97% complete hematologic response and 83% cytogenetic response was documented after many years of regular follow up of CML patients received imatinib [36, 37]. Patients with hematological or cytogenetic resistance to standard dosage of imatinib (400 mg) were begun with tall dosage (600–800 mg). Some of patients are unlikely to be overcome by high doses due to some specific mutations, in these cases alternative target therapy should be considered for patients fails or with suboptimal response [38].

5.2 Dasatinib (Sprycel)

Dasatinib is approved in 2006 as a kinase inhibitor of thiazole carboximide agent and molecular formula C22H26ClIN3O5.S.H2O with highly powerful dual Abl/Src kinase inhibitor against most imatinib-resistant mutants. Dasatinib considering the excellent treatment option for CML cases in chronic phase and other CML phases who develop resistance or fails response to imatinib and for cases with Ph+ ALL [39]. Dasatinib is more than 300 times as powerful as imatinib in restraining unmutated BCR-ABL transcripts in vitro. The incidence of resistance to dasatinib is less than other TKI and the disease progression may be reduced among CML cases treated with dasatinib [40].
5.3 Nilotinib (Tasigna)

Nilotinib is a small molecule tyrosine kinase inhibitor in the form of hydrochloride monohydrate salt and is 20–30 times as potent as imatinib and can be replaced instead of imatinib. In 2007, nilotinib approved by (FDA) for utilize as a particular treatment for Philadelphia chromosome-positive CML (Ph+CML). Nilotinib was statistically superior in both complete cytogenetic response (CCyR) and major molecular response (MMR) (p < 0.001) [41].

5.4 Bosutinib (Bosulif)

FDA approved bosutinib in September 2012, for adult patients with all phases of chronic myeloid leukemia confirmed positive BCR-ABL. Bosutinib is an oral double ABL/SRC kinase inhibitor that is dynamic against numerous BCR-ABL transformations related with imatinib resistance. Bosutinib had the lowest rates of severe side effects, except for diarrhea. In especially, severe cardiovascular side effects were significantly less common in the bosutinib. They experience not complicated to develop blast crisis and progress to accelerated phase in 4% of cases. The overall survival at 2 years were 97% [42].

The suggested dosage of bosutinib is 500 mg oral daily dose with nourishment. The treatment will be proceeded concurring to plan take after up until progression of disease or intolerance of drug.

5.5 Ponatinib (Iclusig)

Ponatinib is approved in December 2012 by the US-FDA as a third generation TKI. Ponatinib is indicated for all phases of CML patients develop resistant to nilotinib or dasatinib or not tolerate to nilotinib or dasatinib and for ALL patients with Philadelphia chromosome positive and resistant to imatinib, dasatinib or nilotinib.

Patients with severely leukocytosis and patients with monocytosis, are less response to tyrosine kinase inhibitors, and have a higher risk of transformation to accelerated and blast phase [43]. The dose of ponatinib recommended daily is 45 mg with modification according to side effects. The recommendations for treatment of CML according to European LeukemiaNet summarized in Table 2.

5.6 Monitoring therapeutic response in CML

The target treatment checking can be performing concurring to inquire about laboratory recommendations for scoring molecular response by utilizing either a cytogenetic or molecular tests, or both, depending on the open facilities. The molecular response to TKI treatment of patients with CML is exceptionally imperative component of CML management with standard take after each 3 months agreeing to ELN guidelines to realize early molecular response playing an imperative part in helpful decision making (Table 3) [45].

The TKI response is the foremost vital prognostic figure. The forecast for CML patients in accelerated and blast phases (AP and BP) is less than that seen in chronic stage (CP). The treatment responses are characterized as optimal, suboptimal or failure. Complete remission accomplished with optimal response which is the most excellent result comparable with that of the common populace. Failure implies that the understanding ought to get a distinctive treatment to restrain the chance of progression of disease and death [46]. Fractional abatement or the problematic response is the intermediate zone between optimal response and failure and usually considered as “warning” for moving to moment line TKI Table 3.
Chronic lymphocytic leukemia (CLL)

Chronic lymphocytic leukemia (chronic lymphoid leukemia CLL), is a heterogeneous disease characterized by the proliferation of functionally incompetent in the peripheral blood, bone marrow, spleen and lymph nodes. CLL is a disease of adult the elder age group as with a median onset at initial diagnosis of 70 and 75 years old and the male to female ratio 2:1 [47].

6.1 Treatment of chronic lymphocytic leukemia

The CLL disease extent and prognosis according to Rai and Binet staging systems. Early stages (0, I, II) and symptomatic patient keep for observation and

**Table 2.**

<table>
<thead>
<tr>
<th>Type</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>Imatinib (400 mg daily) or nilotinib (300 mg twice daily) or dasatinib (100 mg daily)</td>
</tr>
<tr>
<td></td>
<td>HLA type patients and siblings only in case of baseline warnings (high risk, major route CCA/Ph+)</td>
</tr>
<tr>
<td>2nd line, intolerance to the first TKI</td>
<td>Anyone of the other TKIs approved first line (imatinib 400 mg twice daily, nilotinib 400 mg twice daily, dasatinib (70 mg twice daily)</td>
</tr>
<tr>
<td>Second line, failure of imatinib first line</td>
<td>Dasatinib or nilotinib or bosutinib 500 mg daily or ponatinib (45 mg daily)</td>
</tr>
<tr>
<td></td>
<td>HLA type patients and siblings</td>
</tr>
<tr>
<td>2nd line, failure of nilotinib first line</td>
<td>Bosutinib or dasatinib or ponatinib; search for an unrelated stem cell donor; consider AlloSCT and prepare HLA type patients and siblings</td>
</tr>
<tr>
<td>2nd line, dasatinib failure as first line</td>
<td>Bosutinib or nilotinib or ponatinib</td>
</tr>
<tr>
<td></td>
<td>HLA type patients and siblings; search for an unrelated stem cell donor; consider AlloSCT</td>
</tr>
<tr>
<td>3rd line, intolerance or failure to 2 TKIs</td>
<td>Anyone of the remaining TKIs; AlloSCT recommended in all eligible patients</td>
</tr>
<tr>
<td>Any line, T315I mutation</td>
<td>Ponatinib/omacetaxine; consider AlloSCT and search for an unrelated stem cell donor</td>
</tr>
</tbody>
</table>

CCA/Ph+: clonal chromosome abnormalities in Ph+ cells, alloSCT; allogenic stem cell transplantation.

**Table 3.**

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hematological response (CHR)</td>
<td>Normal with disappearance of chronic myeloid leukemia (CML) manifestations</td>
</tr>
<tr>
<td>Complete cytogenetic response (CCyR)</td>
<td>Absence of Philadelphia chromosome (Ph) in 20 of 20 bone marrow metaphases by karyotyping</td>
</tr>
<tr>
<td>Major cytogenetic response (MCyR)</td>
<td>Presence of Philadelphia chromosome in 0–35% of 20 metaphases</td>
</tr>
<tr>
<td>Molecular response</td>
<td>Follow up of quantitative real time PCR (qRT-PCR) analysis, the BCR-ABL1/ABL1 control gene transcript ratio is determined using the International Scale (IS) standardized baseline. ≥3log10 reduction in BCR-ABL1 transcripts (≥0.10% IS) is major molecular response (MMR)</td>
</tr>
<tr>
<td>Optimal response</td>
<td>Complete hematological response (CHR) and ≤35% Ph+ metaphases at 3 months of imatinib therapy, ≤35% Ph+ metaphases at 6 months, CCyR at 12 months and MMR at 18 months</td>
</tr>
<tr>
<td>Suboptimal response</td>
<td>There is no fulfilling criteria for either optimal response or failure. The suboptimal response according to ELN recommendations implies that the long term benefits of imatinib are doubtful</td>
</tr>
<tr>
<td>Failure</td>
<td>There is no complete hematological response at 3 months of imatinib therapy, &gt;95% Ph+ metaphases at 6 months, &gt;35% Ph+ metaphases at 12 months and no MMR at 18 months. Absence of CHR, BCR-ABL1 mutations, clonal cytogenetic evolution, define failure at any time during treatment</td>
</tr>
</tbody>
</table>
Advances in Hematologic Malignancies

regular follow up without treatment. 70% of CLL patients respond to chlorambucil monotherapy which may be given orally for stabilization of leukocytosis and symptoms. Thrombocytopenia in stage IV stabilized with addition of prednisone.

6.2 Purine nucleoside analogous: (fludarabin, deoxycoformycin, 2-chlorodeoxy-adenosine)

Are unique drugs that are effective in low grade lymphomas and chronic lymphatic leukemia.

Fludarabine is active and useful in patients resist to chlorambucil and in newly diagnosed CLL. The alternative use of CVP (Cyclophosphamide, Vincristine and Prednisone). In addition fludarabine and cladribine in treatment of CLL, the combination of rituximab against CD20 and alemtuzumab against CD52, has an acceptable safety profile, and has clinical activity with a short course in patients with refractory or relapsed to chemotherapy.

6.3 Ibrutinib (Imbruvica)

Is a small molecule targeted drug that acts as an irreversible burton tyrosine kinase inhibitor (BTK) and can be used to treat chronic lymphocytic leukemia (CLL). In 2013 FDA approved ibrutinib for treatment patients with mantle cell lymphoma and in 2013 also approved for CLL and small lymphocytic lymphoma with 17p [48, 49].

6.4 Idelalisib (Zydelig)

Is another targeted drug approved for patients with CLL with CD20 positive in combination with rituximab or ofatumumab. It blocks a kinase protein called PI3K. FDA in July 28, 2014, has approved idelalisib 150 mg tablets for the treatment of B-CLL. Idelalisib has been appeared to assist treat CLL after other medications have been attempted and is indicated in combination with rituximab for patients with relapsed chronic lymphocytic leukemia (CLL) and significantly reported excellent response rate, overall survival and progressed progression-free survival (Tables 4 and 5) [50, 51].

6.5 Venetoclax (Venclexa)

Is a selective drug that targets BCL-2, a protein in CLL cells had a manageable response for patients with small lymphocytic lymphoma (SLL) poor prognostic and chronic lymphocytic leukemia whose relapsed or refractory to other drugs (Tables 4 and 5) [52].

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td>MEDI-551</td>
<td>CD19</td>
</tr>
<tr>
<td></td>
<td>Ofatumumab</td>
<td>CD20</td>
</tr>
<tr>
<td></td>
<td>Obinutuzumab</td>
<td>CD20</td>
</tr>
<tr>
<td></td>
<td>Epratuzumab</td>
<td>CD22</td>
</tr>
<tr>
<td></td>
<td>Lucatumumab</td>
<td>CD40</td>
</tr>
<tr>
<td>Antibody drug conjugates</td>
<td>Brentuximab vedotin</td>
<td>CD30</td>
</tr>
<tr>
<td></td>
<td>Polatuzumab vedotin</td>
<td>CD79B</td>
</tr>
<tr>
<td></td>
<td>Inotuzumab ozogamicin</td>
<td>CD22</td>
</tr>
<tr>
<td></td>
<td>SAR3419</td>
<td>CD19</td>
</tr>
</tbody>
</table>

Table 4.
Novel antibodies and antibody-drug conjugates directed against surface antigens [49].
Non-Hodgkin’s lymphomas (NHL)

Non-Hodgkin’s lymphoma is one of the most common hematologic neoplasms and there will be an estimated in USA over 79,000 new cases and over 20,000 deaths in 2018.

Diffuse large B cell lymphoma (CD20+) is the most common type followed by follicular lymphoma and the treatment choices for patients is CHOP protocol with or without Rituximab.

7.1 Rituximab

Rituximab is achimeric anti-CD20 human monoclonal IgG1 effective directly on the surface receptor found on typical pre-B and mature B cell of non-Hodgkin’s lymphoma subtypes, driving to cell cytotoxicity and cell death [53]. It was at first utilized in aggressive and very aggressive relapsed or refractory lymphoma and demonstrated safety with disease regression and free survival [54].

Major toxicities patients with NHL include infusion-related fever chills, fatigue, pruritus, nausea, and vomiting, angioedema, headache, hypotension, bronchospasm, urticaria during the first infusion. Rituximab was approved in November 1997 for medical use of refractory or relapsed lymphoma (B-cell). Rituximab play excellent role in combination with chemotherapy and represents a paradigm shift in treatment of lymphomas and improve the outcome for all CD20+ NHL and CLL [55].

7.2 Radioimmunotherapy

Radioimmunotherapy (RIT) is a safe and effective treatment option that combines the advantages of radiotherapy and immunotherapy and advance the adequacy of anti-CD20 target therapy by combining the antibody with a radioconjugate, yttrium-90 without risk of secondary malignancies.

7.2.1 Ibritumomab tiuxetan

Is a monoclonal antibody of IgG1 kappa with name (Zevalin) and the first radiopharmaceuticals to be approved for patients with NHL of B lymphocytes CD20 molecules. Ibritumomab linking to the metal chelator tiuxetan, a monoclonal antibody (111In Zevalin™, Biogen Idec) stable binding of indium-111 (111In) for radionucleotide tumor possible with 90Y ibritumomab tiuxetan [56].

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune checkpoint inhibitors</td>
<td>Ipilimumab</td>
<td>CTLA-4</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab</td>
<td>PD-1</td>
</tr>
<tr>
<td></td>
<td>Nivolumab</td>
<td>PD-1</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>PD-1</td>
</tr>
<tr>
<td>Small molecule inhibitors</td>
<td>Ibritinib</td>
<td>BTK</td>
</tr>
<tr>
<td></td>
<td>Idelalisib</td>
<td>PI3Kd</td>
</tr>
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<td></td>
<td>Duvelisib</td>
<td>PI3Kd</td>
</tr>
<tr>
<td></td>
<td>Copanlisib</td>
<td>PI3Kd</td>
</tr>
<tr>
<td></td>
<td>Navitoclax</td>
<td>Bcl-2</td>
</tr>
<tr>
<td></td>
<td>Venetoclax</td>
<td>Bcl-2</td>
</tr>
</tbody>
</table>

Table 5.
Novel antibodies directed against immune checkpoint proteins and novel small molecule inhibitors [49].
FDA in February 2002 approved 90Y ibritumomab tiuxetan for treatment of refractory and relapsing indolent follicular lymphoma or transformed lymphoma which include lymphoma refractory to rituximab. The toxicity of ibritumomab tiuxetan is primarily hematologic, which is both transient and reversible. The common side effects, nausea, vomiting, drug interactions, diarrhea, cough and dizziness.

7.2.2 Tositumomab iodine I 131

Is a CD20 radiotherapeutic targets for treatment of lymphoma patients with positive CD20 especially cases of indolent low grade lymphoma, transformed lymphoma, refractory and relapsed lymphoma and lymphoma refractory to rituximab. The therapeutic administration protocol contain two separate products of tositumomab and iodine I131 tositumomab which will be given in two different steps include dosimetric dose and therapeutic dose separated by 10 days interval.

A relapsed, refractory, or transformed indolent low grade lymphoma overall response (OR) rates have ranged from approximately 60–80% and CR rates have ranged from about 20–40% and a median duration of response of 2 years [57]. Tositumomab toxicities include severe and prolonged thrombocytopenia and neutropenia as well as increase risk of developing other diseases include hypothyroidism, myelodysplasia, acute leukemia.

In June 2003, Tositumomab approved by FDA for treatment of CD20+ follicular lymphoma, that was relapsed following chemotherapy or lymphomas refractory to rituximab.

7.3 Denileukin diftitox

Denileukin diftitox (Ontak) is a fusion protein (interleukin 2 and diphtheria toxin) approved by FDA in October 16, 2008, for use as an antineoplastic agent to treat pretreated patients with CD25 positive cutaneous T cell lymphomas that express IL-2 receptors. A phase III clinical trial, had good response and significant improvements in self-rated overall QOL [58].

Denileukin diftitox is available in solution in 2 mL single use vials of 150 μg/mL (300 mcg in 2 mL) under the brand name Ontak. The typical dose of intravenous infusion is 9 or 18 mcg/kg/day given for 8 courses every 3 weeks.

Epratuzumab is an antihuman CD22 IgG1 antibody that targets CD22 antigen, found on the surface of B-lymphocytes antigen, CD22 [59, 60]. This drug, either in single administration or in combination with rituximab, created promising outcomes with complete remission [CR] and an ORR of 67% [49].

7.4 Ofatumumab

In August 2009, ofatumumab was approved as a high-affinity IgG1 mAb that binds to a membrane-proximal epitope of the CD20 molecule of the B cell with potential anti-neoplastic activity triggering and exhibited greater induction of complement-dependent cell lysis (CDCL) and antibody-dependent cell-mediated cytotoxicity (ADCC) of B cells over expressing CD20 when compared with rituximab [61].

7.5 Obinutuzumab

Is a unique monoclonal antibody, designed to attach to CD20 antigen expressed on the surface of pre-B- and mature B-lymphocytes of malignant lymphoma and for maintenance treatment of patients previously untreated low grade lymphoma especially follicular type resulted in significant free survival. The post-translational
glycoengineering process used in the development of this agent, add to its higher binding affinity for human FcγRIII receptors on immune effector cells and the mAbs to novel targets are being developed with ADCC in mind [62].

7.6 Brentuximab vedotin

An anti-CD30 antibody-drug conjugate and demonstrated significant clinical activity in patients with CD30+ malignancies, including Reed Sternberg cells in classical HL and anaplastic large cell lymphoma (ALCL) (Tables 4 and 5).

8. Multiple myeloma

Multiple myeloma (MM) is a blood cancer that remains serious disease and it cannot usually be cured because most patients relapse after treatment or become refractory to the treatments.

Novel agents are as of now in advancement for the management of refractory or relapsed multiple myeloma, counting immunomodulatory drugs, monoclonal antibodies, proteasome inhibitors, cell signaling focused on treatments, and procedures focusing on the tumor infiltration or metastasis.

Proteasome inhibitors such as bortezomib target therapy of multiple myeloma the ubiquitin pathway, coming about in cytotoxic damage due to disturbance of protein corruption in myeloma cells. The immunomodulatory agents, thalidomide, lenalidomide, and pomalidomide, are a novel of class of oral target agents impact on myeloma cells through a few components counting coordinate cytotoxicity, antiangiogenic impacts, and antitumor immunity activation (Figure 1).

8.1 Proteasome inhibitors

The proteasome is a gigantic highly sophisticated protease complex that degrades unneeded or damaged proteins by proteolysis. As such, the proteasome plays an important role in critical cellular processes including proliferation, differentiation, cell cycle progression and survival DNA repair, angiogenesis and apoptosis [63]. Three proteasome inhibitors, carfilzomib, bortezomib and ixazomib are approved by FDA and oprozomib and other agents are in the clinical trials late stages.
8.2 Bortezomib

Bortezomib (Velcade) is the first proteasome inhibitor approved by FDA in May 2003. A trial phase I explored bortezomib for its tolerance and safety in multiple myeloma, lymphoma, leukemia and lung cancers [64]. Bortezomib showed safely tolerability with few side effects such as general weakness, fever, fatigue, decreased sensation and paresthesia, nausea, vomiting and thrombocytopenia. Amazing response rate (35%) and response duration reaching to more than 1 year in intensely pretreated multiple myeloma patients were reported in the SUMMIT phase II trial [65].

8.3 Carfilzomib

Carfilzomib is a new intravenous agent approved by FDA in 2018 for multiple myeloma of proteasome inhibitors like bortezomib. It should be given with dexamethasone or with dexamethasone and lenalidomide in refractory or relapsed multiple myeloma. In differentiate carfilzomib with bortezomib, appears a better selectivity to the proteasome, covering more of the proteolytic subunits. The common side effects are mild to moderate fever, cytopenia, diarrhea, headache and swelling in hands and feet [66].

8.4 Ixazomib

FDA approved ixazomib in 2015 as the first an oral proteasome inhibitor. Ixazomib used in the same time with dexamethasone and lenalidomide for the treatment patients with refractory or relapsed multiple myeloma [67].

8.5 Immunomodulatory drugs (IMiDs)

The presentation of immunomodulatory drugs (IMiDs), assist progressed long-term survival of patients with multiple myeloma. Thalidomide and its derivatives, lenalidomide and pomalidomide possess pleiotropic anti-myeloma properties including immune-modulation, anti-angiogenic, anti-inflammatory and anti-proliferative effects.

8.6 Monoclonal antibodies (MoAbs)

Presentation of the primary mAb different therapy of multiple myeloma started a modern time in multiple myeloma therapy. Daratumumab, focusing on CD38 as an exceedingly and constantly expressed surface antigen of myeloma, is the primary counter acting agent that was approved by the FDA for the treatment of newly-diagnosed multiple myeloma and also for refractory and relapsed myeloma patients [68]. Elotuzumab, targeting signaling lymphocytic activation molecule F7 (SLAMF7), has been endorsed in combination with lenalidomide and dexamethasone for therapy of myeloma patients in relapse or refractory to treatment [69].

8.7 Histone-deacetylase (HDAC) inhibitors

An assortment of epigenetic changes together with hereditary changes is basic for malignant growth and proliferation. Altering acetylation status of histones is, close by DNA methylation, an option to gene alteration and blocks gene transcription and inhibits differentiation, providing a rationale for developing HDAC inhibitors. Panobinostat was excessively attempted with different mixes in a few clinical stage I/II trials.
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