Future Directions in Aggressive Lymphomas

Guilherme F. Perini and Luis E. Fayad

Abstract New exciting discoveries have emerged in the field of aggressive lymphomas. A better understanding of the biology of lymphomas has been translated into clinical practice, and new drugs are emerging as a hope for better disease control. In this chapter, we review the new therapies for aggressive lymphomas, like proteasome inhibitors, B-cell receptor signaling inhibitors (Syk, Burton's tyrosine kinase and protein kinase C inhibitors) and mammalian targets of rapamycin. Moreover, a concise review of the new monoclonal antibodies (MoAbs) and their new targets is presented. Immunomodulatory drugs like lenalidomide also have shown potential benefit in patients with aggressive lymphomas. Although more studies are necessary, these drugs will probably be incorporated in the management of aggressive lymphomas, with less toxic, targeted therapy.

The hematological malignancies have long been in the forefront of development of cancer therapies. The association of new discoveries in genetics and molecular biology has contributed to a better understanding of cancer and consequent treatment innovations. Chronic myeloid leukemia (CML) remains a paradigm of the foresaid. From the Philadelphia chromosome, the first chromosome-specific abnormality related to cancer [1], to the consequent discovery of the BCR-ABL, a fusion protein with abnormal kinase activity responsible for the proliferation of myeloid cells [2], a new era in cancer biology has emerged. Not long, patients with CML could benefit from these discoveries: imatinib (Gleevec®), a selective inhibitor of tyrosine kinase,

G.F. Perini (✉)
Department of Hematology, Hospital Israelita Albert Einstein,
Avenida Albert Einstein, 627—Morumbi, Sao Paulo 05652-900, Brazil
e-mail: guiperini@einstein.br

L.E. Fayad
Department of Lymphoma/Myeloma, University of Texas M.D Anderson Cancer Center,
Houston, TX, USA

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has been the first approved molecular targeted therapy in cancer and is now considered standard therapy for patients with CML [3].

New exciting discoveries also emerged in the field of lymphomas. Rituximab (Rituxan®), a chimeric monoclonal antibody targeted at the CD20 epitope present in B cells, has brought to attention the role of immunotherapy in cancer treatment and is now considered essential in the treatment of most B-cell lymphomas [4]. New monoclonal antibodies (MoAb) have been developed for other malignancies, such as acute myeloid leukemia and renal and pulmonary cancer [5, 6]. Conjugation of a radionuclide with MoAbs introduced the conception of radioimmunotherapy, now available for treatment of selected patients with lymphoma [7].

In the past, aggressive lymphomas were considered an obscure disease with a dismal prognosis. Recent discoveries have shed new light, and aggressive lymphomas are now a treatable and curable disease.

New Insights in the Biology of Aggressive Lymphomas

In the past, the diagnosis of lymphoma and cancer in general relied mostly on morphologic features. However, the findings of recurrent cytogenetic abnormalities and consequent molecular alterations, urged the need of more refined diagnosis. Mantle cell lymphoma, for example, is now recognized as a molecular-defined lymphoma, with over expression of cyclin D1, a consequence of the t(11;14) present in malignant cells [8]. In contrast, the diagnosis of diffuse large B-cell lymphoma (DLBCL), the most common subtype of lymphoma, remains confined to morphological and immunohistochemical findings. Consequently, it is reasonable to conclude that different types of DLBCL, with diverse molecular alterations and clinical behavior, are diagnosed and treated the same.

An area of great interest in recent research is the attempt to divide different subtypes of DLBCL [9]. Recently, great interest have been directed to subtypes of aggressive DLBCL-associated MYC rearrangements. Overexpression of *c*-MYC drives cell proliferation and the expression of other genes involved in cell growth, and patients with DLBCL with c-MYC expression usually have high-grade morphologic features that morphologically resemble Burkitt lymphoma (BL) [10]. A subgroup of patients also presents concurrent translocations involving the BCL-2 gene. This subtype of lymphomas, so-called “double hit” DLBCL, usually present with very aggressive disease, with bone marrow involvement, elevated lactate dehydrogenase levels, and multiple extranodal sites [11, 12]. Patients seldom respond to chemotherapy, and those who achieve a response subsequently suffer an early relapse [13]. Studies are being conducted to evaluate the role of intensified chemotherapy in this subset of patients.

Gene profile expression studies have contributed to a better understanding and separation of at least two subtypes of DLBCL: germinal center B-cell (GCB) and activated B-cell (ABC) lymphomas [14]. When the clinical outcome of the cases was examined, cases with the GBC signature had a significantly better prognosis

than the cases that expresses the ABC signature [15]. Although the initial studies were conducted in the era pre-rituximab, subsequent studies confirmed the prognostic value of the GCB-cell signature [16]. Subsequent studies have focused on the genes expressed in the GCB or ABC subtypes. High expression of a proliferation signature and low expression of major histocompatibility complex signature are associated with poor survival. Interestingly, studies focusing on the lymph node stromal signature disclosed a potential prognostic value [17]. High expression of stromal signatures associated with extracellular matrix deposition and tissue inflammation (stromal I signature) is associated with better outcome than cases with high expression of signatures associated with angiogenesis (stromal II signature) [18]. Other studies on subsets of DLBCL based on site of presentation also show different patterns of gene expression.

Although these studies have shown the potential of gene expression to define oncogenic pathways, it has yet to be translated in clinical practice. However, new studies have shown that a subset of DLBCL may benefit from a specific therapy. For instance, the Biocoral study, a post hoc study of biological variables of the CORAL study, has shown that patients with relapsed DLBCL with GCB phenotype have better outcomes when treated with R-DHAP instead of R-ICE [19].

Imaging in Aggressive Lymphomas

The traditional approach to treatment monitoring through imaging has relied on anatomical changes assessing tumor size before and after treatment. This approach has proven through time to be rather problematic. The rate of structural regression of tumors after chemotherapy depends on several factors in the host, as well as the amount of fibrosis present in the tumor. Moreover, the response criteria universally adopted are somewhat arbitrary, and a consistent correlation between tumor response and patient survival has not been demonstrated.

Over 50 years ago, Otto Heinrich Warburg discovered that malignant cancers ferment glucose to lactic acid much more rapidly than most normal cells [20]. The latter, known as the "Warburg effect," is the basis for the use of fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET-CT) for the staging and treatment monitoring of a variety of cancers [21–23]. The first reports of PET-CT for lymphoma imaging were published more than 20 years ago, and during the last decade, PET-CT has been introduced into all of the steps of lymphoma management.

In aggressive lymphomas, PET-CT has proved to be highly sensitive in determining sites of disease [24, 25]. Several studies have demonstrated the superiority of PET-CT for monitoring treatment of aggressive NHL [24–26]. Patients with a negative PET-CT after treatment have better progression-free survival [27]. However, the role of interim PET-CT in DLBCL patients is controversial, with studies showing conflicting results [28, 29]. Outside clinical trials, interim PET-CT is not recommended in patients with DLBCL.

Recent trials are now focusing on PET-CT-tailored strategies. The Groupe d'Etude des Lymphomes de l'Adulte (GELA) is currently conducting a phase III trial of salvage autologous stem cell transplantation (ASCT) if PET results are positive after two cycles of R-CHOP [30]. In the same manner, the British Columbia Cancer Agency is testing four cycles of R-ICE if PET results are positive after four cycles of R-CHOP [31]. The Alberta Cancer Board also conducted a trial of PET-CT-guided treatment and preliminary results suggest that high-dose therapy with R-DICEP and ASCT may improve EFS for poor prognosis DLBCL with interim positive PET-CT [32].

New Treatments in Aggressive Lymphomas

The development of new drugs as well as incorporation of drugs already developed for other malignancies shows promising results in aggressive results.

Proteasome Inhibitors

The proteasome is a multi-subunit protease complex responsible for the elimination of intracellular proteins tagged for degradation [33]. The ubiquitin-proteasome pathway controls protein function through the degradation of polyubiquitinated intracellular proteins, involved in cell cycle regulation, transcription factor activation, and apoptosis [34, 35]. Diverse types of cancer cells undergo apoptosis in response to proteasome inhibition, and many proteins involved in lymphomagenesis are regulated by the proteasome pathway, including cyclins, NF-κB and p53 [36–38].

NF-κB is a family of proteins that control genes implicated in cell activation, proliferation, and apoptosis [39]. Several studies have implicated increased NF-κB activity in different lymphomas, such as MALT lymphomas [40], peripheral T-cell lymphoma [41], and activated B cell-like DLBCL [42]. Bortezomib (Velcade®), a 20S proteasome subunit inhibitor approved for the treatment of relapsed refractory multiple myeloma, has also shown activity in NHL [43]. A phase II trial of 155 pretreated patients with MCL receiving bortezomib (PINNACLE) reported an ORR of 31%, with 14 patients with CR/Cru [44]. Based on this trial, bortezomib is now approved for patients with relapsed/refractory MCL. The role of bortezomib in association with standard chemotherapy for untreated patients with MCL is being evaluated.

Bortezomib has also been studied in patients with DLBCL, with modest activity as a single agent. The association of bortezomib with standard R-CHOP (BR-CHOP) therapy was evaluated in a phase II prospective trial with 76 patients with DLBCL and MCL (40 patients with DLBCL). BR-CHOP resulted in an intent-to-treat response of 88% [45]. The addition of bortezomib in salvage therapy of patients with DLBCL has also been evaluated. Relapsed patients with ABC subtype of DLBCL were treated with bortezomib in combination with dose-adjusted EPOCH chemotherapy. The ORR was 83%, with an OS of 10.8 months [46]. Two prospective

trials (LYM2034 and PYRAMID) are assessing the role of bortezomib combined with chemotherapy in upfront therapy of patients with non-GCB DLBCL.

B-Cell Receptor Signaling Inhibitors

B-cell receptor (BCR) plays an important role in normal B-cell development. Progenitor B cells only differentiate into mature B cells if they express a functional BCR, and those B cells that fail to express a BCR undergo apoptosis. Antigen BCR ligation activates a family of tyrosine kinases, named Scr protein kinases. These tyrosine kinases consequently recruit Syk, another tyrosine kinase responsible for activation of several other molecules, including protein kinase C (PKC), phosphatidyl-inositol-3-kinase (PI3K) and AKT (also known as protein kinase B) [47]. In DLBCL, a chronically "tonic signaling" has been observed and gene expression profiling studies have shown that some DLBCL have overexpression of the BCR, indicating a dependence on this signaling pathway [48]. New drugs targeting the BCR signaling pathway are being developed.

Syk Inhibitors

In vitro studies have confirmed the presence of deregulated Syk pathway in DLBCL [49]. Furthermore, in vitro inhibition of Syk induced apoptosis of DLBCL cell lines. Syk inhibitors are now testing the possible therapeutic effect of these drugs.

Fostamatinib disodium (R406), an oral ATP-competitive Syk inhibitor, is the first to be tested in clinical trials. In preclinical studies, R406 inhibited the proliferation and induced apoptosis of DLBCL lines with tonic BCR signaling, especially lines with high expression of cell-surface immunoglobulin [48]. A phase I/II trial including 68 patients with relapsed NHL (23 DLCBL) showed promising results, including a 22% clinical response in DLBCL, with four partial responses and one complete response [50]. Adverse events were mild and included fatigue, gastrointestinal symptoms, and myelosuppression. Further studies both as single agent and in combination with other drugs are being conducted. Moreover, it has been demonstrated that some patients with peripheral T-cell lymphoma also have a deregulated Syk pathway [51], and studies are conducted with fostamatinib in these patients.

Bruton Tyrosine Kinase Inhibitors

Bruton agammaglobulinemia, an X-linked agammaglobulinemia first described in 1952, is caused by mutations in the gene coding for Bruton tyrosine kinase (BTK). Patients with Bruton agammaglobulinemia have profound hypogammaglobulinemia, with fewer than 1% of the normal number of B cells, with an immature phenotype [52].

Another approach to interrupting BCR signaling is with BTK inhibitors. BTK is a component of the BCR signaling pathway and is downstream of Syk. BTK is critical to the maturation of pre-B cells to differentiating mature B cells [52]. Findings suggest that BTK may be an essential transducer of signals that govern immunoglobulin rearrangement events and re-expression of the RAG gene products. BTK signaling may also regulate the survival of immature B cells that have performed a successful Ig light chain rearrangement, as well as governing the entrance of B cells in the follicular center [53].

Targeting BTK is a promising new therapeutic approach in NHL. Ibrutinib (PCI-32765), an oral irreversible BTK inhibitor, has been tested in a phase Ib/II follow-up trial in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma and showed an ORR of 70%, in a 10 month follow-up [54]. An interim analysis of a phase II study in 48 patients with relapsed/refractory mantle cell lymphoma showed an overall response rate of 67%. Interestingly, patients exposed to bortezomib had higher rates of response (75% vs. 58%) [55].

Ibrutinib has also been tested in patients with relapsed/refractory ABC DLBCL. In an interim analysis of a phase I/II study, eight patients received ibrutinib in a fixed dose of 560 mg daily for 35 days. Two patients achieved CR, and other three patients achieved stable disease (SD), showing that ibrutinib has clinical activity in aggressive lymphomas [56].

PKC Inhibitors

The PKC family is composed of four main members: conventional PKCs (α, β and γ), novel PKCs, atypical PKCs, and PKC-related kinases. PKC-β protein is a critical component of the BCR signaling pathway and is related to cell survival by activation of the NF-κB complex [57]. PCK-β has also been related in VEGF-mediated angiogenesis [58]. Since both NF-κB and VEGF are implicated with DLBCL, PKC-β is an attractive target for development of new drugs.

Enzastaurin is an oral ATP-competitive selective inhibitor of PKC-β that also targets the PI3K-AKT pathway and has shown proapoptotic, antiproliferative, and antiangiogenic activities in several cancer lines [59]. A phase II trial including 55 patients with relapsed DLBCL disclosed a safe toxicity profile, with rare hematological toxicities. The primary endpoint was freedom from progression after two cycles, and 22% of patients achieved this endpoint, including three patients achieving CR lasting more than 20 months [60]. A phase III trial is testing enzaustarin in combination with R-CHOP for first-line treatment of patients with DLBCL. Enzastaurin maintenance is also being tested in high-risk DLBCL patients achieving a CR after R-CHOP treatment [61].

Bryostatin 1 (B-1) is a modulator of the PKC family and has shown antitumor activity in vitro. An immunomodulatory component is also present, with neutrophil and immune cell activation. Studies in patients with CLL or indolent NHLs are being conducted, exploring the effect of B-1 in combination with other cytotoxic agents [62].

Heat Shock Protein Inhibitors

Heat shock proteins (HSP) are cytosolic molecules responsible for chaperoning multiple proteins necessary for cell signaling, proliferation, and survival [63]. In the presence of cellular stress, an increase in the expression of HSP occurs, and HSP bind to client proteins protecting them from degradation and preserving cells from apoptosis [64].

HSP90, a member of the HSP family, is overexpressed in cancer cells and may be involved in the survival advantage of these cells. Moreover, HSP90 is overexpressed in many NHL subsets, including DLBCL, and is related to histological transformation of indolent lymphomas [65]. Geldanamycin (17-allylamino-17-demethoxygeldanamycin [17-AAG]) is the first HSP90 inhibitor tested in humans. It has shown to induce cell cycle arrest and apoptosis through the downregulation of cyclin-dependent kinase 1 and AKT and the activation of caspase 9 in MCL cell lines [66]. A number of phase I trials with 17-AAG and similars have shown some activity in melanoma [67], myeloma [68], or breast cancer [69]. Phase I studies in patients with relapsed or refractory NHL are ongoing.

Mammalian Target of Rapamycin Inhibitors

Mammalian target of rapamycin (mTOR) is a kinase involved in regulation of proliferation, cell growth, and apoptosis. The activation of the PI3K-AKT-mTOR pathway promotes the translation of proteins that regulate cell cycle, in particular the eukaryotic initiation factor 4E-binding protein 1 and the p70S6 kinase, responsible for the translation of cyclin D1, c-MYC, and Stat3 proteins, all involved in the pathogenesis of NHL [70]. The PI3K pathway is constitutively activated in the majority of B-cell lymphomas, as manifested by phosphorylation of S6K and 4E-BP1 [71]. Moreover, mTOR inhibitors can decrease the expression of cyclin D1 and cyclin/cyclin-dependent kinases, an interesting property for the treatment of MCL [72].

Two rapamycin analogs, temsirolimus and everolimus, have proved to produce growth inhibition in a broad range of tumor models, including lymphoma. Rapamycin and temsirolimus have demonstrated antitumor activity in vitro against a variety of lymphoma cell lines, especially in MCL cells [73]. In a phase II trial with 35 patients with relapsed/refractory MCL, temsirolimus was delivered as a weekly 250 mg intravenous infusion, and showed an ORR of 38%, including 1 CR [74]. The most significant myelosuppression was thrombocytopenia, and the study was repeated with additional patients receiving 25 mg temsirolimus intravenously every week. An ORR of 41% was observed, with lower incidence of thrombocytopenia.

A phase III trial, comparing temsirolimus with investigator's choice of conventional chemotherapy for patients with relapsed/refractory MCL showed better PFS and ORR in patients treated with temsirolimus [75]. In another phase II trial, temsirolimus was combined with rituximab in 71 patients with MCL exposed to rituximab.

The ORR was 48%, with 20% (14 of 71) complete responses, and 28% (20 of 71) partial responses [76]. A phase I trial for new, untreated MCL patients is being conducted, combining rituximab, temsirolimus, and cladribine for patients not transplant eligible.

Everolimus, an oral mTORC1 inhibitor, has also shown antitumor effects. Preclinical studies have shown that everolimus inhibits phosphorylation of mTOR substrates and induces G1 arrest [77]. Moreover, everolimus can sensitize MCL cells to cytotoxic agents, including doxorubicin and bortezomib. Hodgkin lymphoma cells also show activation of the PI3K pathway and are sensitive to everolimus [78]. A phase II trial evaluated everolimus in 37 patients with refractory/relapsed aggressive NHL, including 20 patients with DLBCL and 14 with MCL. The ORR was 32%, with a median duration of response of 3.1 months [79]. Everolimus was well tolerated, despite mild hematological toxicity. Subsequent studies have demonstrated positive results in patients with CLL/SLL [80] and Waldenstrom macroglobulinemia [81]. mTOR inhibitors also have activity in relapsed, aggressive lymphomas. In a phase II study, 47 patients with relapsed DLBCL were treated with single-agent everolimus with an ORR of 30%. Interestingly, an ORR of 63% was observed in relapsed T-cell NHL [82].

In conclusion, the mTOR inhibitors temsirolimus and everolimus have modest single-agent activity in NHL, CLL/SLL, Hodgkin lymphoma, and Waldenstrom macroglobulinemia. These agents are now being tested in larger single-agent studies as consolidation after induction therapy for DLBCL, as treatment for new untreated Waldenstrom macroglobulinemia, relapsed Hodgkin lymphoma, and in combination with chemoimmunotherapy for untreated MCL.

Histone Deacetylase Inhibitors

Histones are small basic proteins that form the nucleosome core by binding to DNA. Histone acetylation is relevant in diverse cellular mechanisms, including chromatin assembly, DNA repair, and gene expression. In a general way, histone acetylation is linked to a relaxed chromatin status, with activation of transcriptional activity. Histone deacetylation, however, causes condensation of the chromatin and repression of transcriptional activity [83]. An imbalance in these mechanisms is involved in the pathogenesis of different tumors. In NHL, the frequent translocation affecting the BCL6 gene activates the HDAC-containing complex and inhibits transcription and differentiation of germinal center B cells [84].

Several histone deacetylase inhibitors (HDAC) are available for treatment of hematological malignancies. Vorinostat (Zolinza®, SAHA) is a HDAC inhibitor approved for the treatment of relapsed cutaneous T-cell lymphomas [85]. A phase II trial of vorinostat in 18 patients with relapsed DLBCL showed modest activity, with only one patient achieving CR [86].

MGCD0103 (mocetinostat) is an oral HDAC inhibitor under study. An interim analysis of a phase II trial in 50 patients with relapsed/refractory DLCBL and FL reported an ORR of 23.5% in DLBCL, with one CR and three PR [87]. Mocetinostat is also being evaluated for patients with HL. Panobinostat, a novel HDAC, inhibits proliferation and induces apoptosis in tumor cell lines. Interestingly, a synergic effect with mTOR inhibitors has been demonstrated [88], and phase I/II trials of panobinostat associated with everolimus are being conducted for patients with relapsed/refractory NHL.

Immunomodulatory Drugs

Immunomodulatory drugs (IMiDs) are a group of compounds structurally and functionally related to thalidomide, an oral sedative with anti-inflammatory properties. Thalidomide interferes with tumor microenvironment and inhibits tumor necrosis factor TNF-α through degradation of its mRNA, as well as IL-6, IL-1, E-selectin, L-selectin, and GM-CSF [89, 90]. Thalidome also stimulates T-cell lymphocytes, inducing proliferation, cytokine production, and cytotoxic activity and upregulates natural killer (NK) cell activity [91]. Furthermore, thalidomide exhibits antiangiogenenic properties, by decreasing expression of vascular endothelial growth factor (VEGF) [92].

Lenalidomide (Revlimid®), a less toxic and more potent IMiD, is extensively used in multiple myeloma [93, 94], and recent clinical studies show promising results in NHL. A phase II trial of single-agent lenalidomide included 49 patients with aggressive NHL, including MCL and DLBCL. The ORR was 35% in all patients and 28% in DLBCL patients [95]. Patients with MCL also showed responses with lenalidomide in combination with rituximab [96]. A phase I/II trial combining lenalidomide with standard R-CHOP (R2-CHOP) in aggressive lymphoma patients has shown a secure toxicity profile, with no major effects or hematological recovery delays. Moreover, for 30 patients evaluable for response, the overall and complete response rate was 100% and 83%, respectively [97]. Lenalidomide may also have distinct activity depending on the GBC/ABC phenotype. In a retrospective study of patients treated with salvage lenalidomide, the overall response rate in patients with non-GCB subtype was superior to the GCB phenotype [98].

Novel Monoclonal Antibodies

Since the introduction of rituximab in the treatment of lymphomas, research has focused on the development of novel monoclonal antibodies. Strategies have been divided in two different groups: improving anti-CD20 activity and development of new targets for immunotherapy.

New Anti-CD20 MoAbs

Ofatumumab (Arzerra®), a fully human IgG anti-CD20 antibody, targets a different epitope within the CD20 molecule, responsible for different therapeutic properties. Compared with rituximab, ofatumumab binds in a region closer to cell membrane, improving binding stability [99]. Moreover, stronger complement-dependent cell lysis (CDC) is observed with ofatumumab, with similar antibody-dependent cellular toxicity (ADCC) [100]. Ofatumumab was tested as monotherapy in patients with FL in a phase I/II trial, with ORR of 13% and an ORR of 22% in patients refractory to rituximab [101]. These encouraging results led to a trial in heavily pretreated patients with relapsed/refractory aggressive B-cell NHL, most of them preexposed to rituximab. Overall response rates reached 11% (three complete responses and six partial responses) [102].

Veltuzumab is also a second-generation of anti-CD20 MoAbs, developed to improve the efficacy of rituximab. Veltuzumab is a humanized antibody with structural differences compared with rituximab and shows similar in vitro CDC and ADCC properties, with a slower dissociation from the CD20 epitope. Moreover, veltuzumab has shown enhanced tumor B-cell depletion compared with rituximab. A recent phase I/II study in patients with relapsed/refractory different subtypes of NHL showed an ORR of 44 and 27% CR [103]. Interestingly, in the DLBCL patients, a PR of 43% was observed, all of them previously treated with R-CHOP.

Obinutuzumab (GA101), a humanized anti-CD20, has specific modifications in the Fc and hinge regions, leading to a high binding affinity to a distinct CD20 epitope and significant increase in FcgRIII receptor binding. These particular alterations result in a superior ADCC and reduced CDC activity. Moreover, obinutuzumab is thought to increase signaling in target cells, activating apoptotic pathways. A superior antitumor activity of GA101 over rituximab has been suggested by studies in animal models of lymphoma [104]. A phase I/II trial of GA101 in relapsed patients with NHL, mostly FL, showed a safe toxicity profile, with ORR of 58% in 12 patients (three CRs and four PRs). In a study with 40 relapsed/refractory aggressive lymphoma patients, an ORR of 30% was observed in DLBCL patients [105].

New Targeted MoAbs

Epratuzumab is a humanized IgG1 anti-CD22 antibody, a protein expressed on the membrane of normal and malignant B cells. CD22 is internalized when it interacts with its natural ligand, and its precise role in B cells is unclear. Epratuzumab shows ADCC and CDC activities, and a phase I/II trial with epratuzumab associated with rituximab showed impressive results in patients with indolent NHL, including CR in patients previously exposed to rituximab. A multicenter phase II trial combining epratuzumab with standard R-CHOP was conducted in patients with DLBCL. Seventy-eight eligible patients were treated with ER-CHOP, with ORR of 95 and 73% CR [106].

Galiximab is a new chimeric IgG MoAb directed against CD80, with synergy effects with rituximab. CD80 is a T-cell co-stimulatory molecule expressed in normal and malignant B cells, and cross-linking of CD80 induces caspase-dependent apoptosis in lymphoma cell lines. Clinical activity of galiximab has been proved mostly in FL, with phase I/II study showing ORR of 64% when associated with rituximab [107].

SGN-40 (dacetuzumab) is also a new and promising MoAb. CD40 is a critical molecule of the TNF family, involved in normal B-cell activation, proliferation, and differentiation. Preclinical studies in human lymphoma cells have shown ADCC activity, as well as cell growth inhibition and apoptosis promotion. After a phase I trial with 35 patients with NHL reporting a safe profile and clinical activity [108], two phase II trials are ongoing with patients with relapsed DLBCL, either as single agent or in combination with chemotherapy. Hence, a phase 1 clinical trial of SGN-40 in combination with rituximab and gemcitabine showed multiple responses in patients with relapsed DLBCL [109].

Blinatumomab is a bi-specific antibody targeting CD19 (B-cell marker) and CD3 (a T-cell engager). Upon binding and engaging both cells, the B cell is stimulated to growth arrest and apoptosis, and T cell is driven to proliferate. In a phase I study with 12 patients with lymphoma, 11 patients had an objective response, and at least half of the responders remained in response at 1 year out of therapy [110].

Inotuzumab ozogamicin is an antibody against CD22 conjugated with calicheamicin, a cytotoxic agent. In a phase I study, responses of 39% were observed in patients with lymphoma, including a 15% response in DLBCL patients. A combination of rituximab with inotuzumab ozogamicin has been tested in patients with recurrent DLBCL, with an ORR of 80%. However, in rituximab-refractory patients, the ORR was much lower (20%) [111].

Conclusion

It has been said that normal lymphocyte differentiation is, in some sense, a disaster waiting to happen [112]. The consequence of this “disaster” is the outbreak of clonal, unorganized, and rapid multiplying malignant B cells. For many years, the use of drugs with cytotoxic effect remained the principle of lymphoma therapy. Outstanding results were achieved with this strategy in some NHL, and a relatively significant proportion of patients could be cured. However, toxicity and late side effects compromised the majority of patients.

Modern oncology is one of the most fascinating areas or research in present years. Knowledge from basic sciences has progressively been translated in clinical outsets. Less toxic, targeted therapy has emerged as a promising approach in lymphoma patients. The understanding of molecular pathways involved in the pathogenesis and clinical behavior of lymphomas has served as foundation for new drug development. Many patients, including the considered nonfit ones, may rely on these new drugs for disease control.

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