Novel Therapeutics for Aggressive Non-Hodgkin's Lymphoma

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ABSTRACT

Application of advances in genomic and proteomic technologies has provided molecular insights into distinct types of aggressive B- and T-cell non-Hodgkin's lymphomas (NHLs). This has led to the validation of novel biomarkers of classification, risk-stratification, and druggable targets. The promise of novel treatments from genomic research has been slow to materialize because of the lack of a therapeutic signature for the distinct NHL subtypes. Patients with lymphoma with aggressive disease urgently require the development of novel therapies on the basis of investigation of dysregulated intracellular oncogenic processes that arise during lymphomagenesis. Although monoclonal antibodies have made significant contributions to the armamentarium of B-cell NHL therapy (eg, anti-CD20), parallel development of small-molecule inhibitors (SMIs) to intracellular targets has lagged behind. Despite these deficiencies, several promising anti-NHL therapies are in development that target immune kinases of the B-cell receptor signaling pathway, mammalian target of rapamycin complex, proteasome, DNA/histone epigenetic complex, antiapoptosis, neoangiogenesis, and immune modulation. This review focuses on novel SMI therapeutic strategies that target overlapping core oncogenic pathways in the context of the 10 hallmarks of cancer. Furthermore, we have developed the concept of a therapeutic signature using the 10 hallmarks of cancer, which may be incorporated into novel phase I/II drug development programs.

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INTRODUCTION

Aggressive non-Hodgkin's lymphoma (NHL) includes diffuse large B-cell lymphoma (DLBCL), mantle-cell lymphoma (MCL), Burkitt's lymphoma, transformed follicular lymphoma (TFL), and peripheral T-cell lymphoma (PTCL), which demonstrate disparate responses to standard chemotherapy regimens. Progress has been made in the management of patients with DLBCL with rituximab added to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)¹ and those with FL with rituximab plus bendamustine.² Despite therapeutic advances, more than 50% of patients with aggressive B-cell NHL (B-NHL) are incurable.³ In PTCL, there is no agent that significantly changes the natural course of the disease; it remains a therapeutic challenge.⁴

Genetic defects intrinsic to B-cell development (eg, variable-diversity-joining, class switch recombination, somatic hypermutation) arising in the immunoglobulin (Ig) loci promote a stepwise accumulation of molecular alterations in the multistep process of lymphomagenesis.⁵ DLBCL, a heterogeneous disease, has numerous genetic alterations (eg, *BCL2*, *BCL6*, *MYC*, *p53*, *PIM-1/2*, *NF-κB*, *CARD11*) residing within two molecular signatures (ie, germi-

nal center B-like [GCB], activated B-like [ABC]) by gene expression profiling that provide diagnostic and prognostic information.^{5,6} These two subgroups have different outcomes with CHOP and R-CHOP therapy, favoring the GCB subtype.^{3,7} A multivariate survival predictor model developed based on patients who received CHOP or R-CHOP identified GC, stromal-1, and stromal-2 signatures.⁷ In other aggressive B-NHL subtypes, cell-cycle defects have been identified. In Burkitt's lymphoma, *c-MYC* promotes antiapoptosis through disturbances in the *p53-MDM2* and *BIM-BCL2* axis.⁸ In MCL, overexpression of cyclin D1 with additional genetic changes (eg, loss of *p16*, mutated *p53*, *ATM* haploinsufficiency) disrupts the cell cycle, compromising the DNA damage response with aberrant proliferation.^{9,10} FL of any grade can transform to a more aggressive DLBCL (ie, TFL), with poor response to therapy and rapid death. The key molecular aberrations are in cell-cycle regulation (eg, *p53*, *MYC*, *BCL6*, *p15*, *p16*) and antiapoptosis (eg, *BCL2*, *BCL3*).¹¹ PTCL involves aggressive heterogeneous tumors with a poor correlation between cytomorphology and prognosis. Molecular genetic studies in PTCL define defects in proliferation (nuclear factor kappa B [NF-κB], Aurora A, Nek2, spleen tyrosine kinase [Syk]), neoangiogenesis (platelet-derived

Table 1. Ten Hallmarks, Targets, and Therapies for B-NHL

Hallmark of Cancer	Therapeutic Target	Treatment
Self-sufficiency in growth signals (proliferation)	Syk, <i>Btk</i> , PKC β , mTORC	FosD, PCI-32765, enzastaurin, temsirolimus, everolimus, deforolimus
Insensitivity to growth-inhibitory signals	HDAC, DNMT	Vorinostat, mocetinostat, romidepsin, panabinstat, belinostat, vidaza
Evading apoptosis	BCL2/BCLX _L , MCL-1, survivin	ABT-263, obatoclax, YM155
Limitless replicative potential	CDK, PARP (hTERT)	AT7519, AZD7762, AT9283, BSI-201
Neoangiogenesis	VEGFR, PDGFR, FGFR	Sorafenib, sunitinib, imatinib, cediranib
Invasion/metastasis	Src, Fak, TGF β	Dasatinib, XL228, TAE226, PF-562271, LY2109761
Immune evasion	NK/T cells (multiple)	Lenalidomide, pomalidomide
Stress response	Proteasome	Bortezomib, carfilzomib
Stromal subversion	SHh, Wnt, Notch	GDC-0449, XL139, XAV939, MK-0752
Serum cytokine response	CXCR4, IL-21R	AMD3100, BKT140, IL-21

Abbreviations: B-NHL, B-cell non-Hodgkin's lymphoma; Syk, spleen tyrosine kinase; *Btk*, Bruton's tyrosine kinase; PKC β , protein kinase C beta; mTORC, mammalian target of rapamycin complex; FosD, fostamatinib disodium; HDAC, histone deacetylase; DNMT, DNA methyltransferase; BCL, B-cell lymphoma; CDK, cyclin-dependent kinase; PARP, poly(ADP-ribose) polymerase; hTERT, human telomerase reverse transcriptase; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; TGF β , transforming growth factor beta; NK, natural killer; SHh, Sonic hedgehog; IL, interleukin.

growth factor receptor [PDGFR]),¹² antiapoptosis (*BCL2*, *PD-1*), and invasion/metastasis (*c-MET*).^{12,13}

Novel drugs are being evaluated in treatment-resistant NHL as single agents and/or in combination with chemotherapy.³ These small-molecule inhibitors (SMIs) target protein kinases (Syk, Bruton's tyrosine kinase [*Btk*], protein kinase C beta [PKC β]), tumor microenvironment (immune modulation), epigenetic complexes (histone deacetylase), protein homeostasis (proteasome), oncogenic signaling pathways (mammalian target of rapamycin complex [mTORC]), cell surface targets (CD20, CD22, CD40, CD80) and angiogenesis (vascular endothelial growth factor [VEGF]). The major challenge is to demonstrate the mechanism of action—guided integration of novel agents into current treatments or alternatively to develop novel combinations with an enhanced therapeutic window.

TEN HALLMARKS OF NHL

NHL with distinct genetic lesions has six essential alterations in cell physiology that seem to collectively dictate the malignant phenotype. The cellular processes are self-sufficiency in growth signals (oncogene addiction), insensitivity to growth inhibitory signals (loss of tumor suppressors), evading programmed cell death, limitless replication potential, sustained angiogenesis, and invasion/metastasis.¹⁴ Two additional hallmarks have been proposed based on evading immune surveillance¹⁵ and malignancy-related stress response.¹⁶ For decades, NHL was studied by isolating malignant cells and ignoring the comalignant stromal components. NHL involves molecular and phenotypic heterogeneity, stem/progenitor cells, and variable sensitivity to therapy implying pre-existing mechanisms of drug resistance. Two additional hallmarks are stromal subversion and immune-inflammatory serum cytokine response promoting tumor proliferation.¹⁷ Mutations arising within stromal fibroblasts and elaboration of paracrine factors promote growth and proliferation of NHL cells. Hence, rational targeting of the 10 hallmarks (Table 1) of NHL provides a strategy for designing novel treatment paradigms for better outcomes and opportunities to elucidate undiscovered biology.

Targets and Therapies for B-NHL

Diagnostic and prognostic signature studies of B-NHL have uncovered potential targets, such as VEGF, CXCR4, connective tissue growth factor (CTGF), NF- κ B,⁷ and PKC β ,¹⁸ but have failed to define a therapeutic signature. A therapeutic signature is an ensemble of druggable targets specific to a B-NHL or T-cell NHL (T-NHL) subtype that are mutated and/or overexpressed within overlapping oncogenic pathways in the context of the hallmarks of cancer. We identified a therapeutic signature for DLBCL (eg, *LCK*, *LYN*, *PIM-1/2*, *c-MET*, *SYK*, *BCL2A1*, *NF- κ B2*) amenable to small-molecule inhibition.¹² A framework for such an approach with existing agents is described in the discussion (Table 2; Fig 1) in the 10 Hallmarks of NHL section. For brevity, major adverse events of each drug are included in Table 2.

1. Inhibition of Proliferation

Uncontrolled activation and proliferation of B-cells via chronic active B-cell antigen receptor (BCR) signaling comprise a key survival pathway in aggressive B-NHL.⁴³ Membrane Ig in combination with antigen-binding IgA/IgB (CD79a/CD79b) heterodimer leads via BCR aggregation and activation of CD79a/b, which transduces amplified signals sequentially via Src family tyrosine kinases Lyn, Syk and *Btk*, initiating a complex signaling cascade with distinct outcomes (Fig 1). Hence, blocking aberrant BCR signaling to immune kinases with SMIs is a key strategy in B-NHL therapy.

Syk inhibitor fostamatinib disodium. Preclinical studies in B-NHL cells and tumors have shown that Syk inhibition induces apoptosis. In a phase I/II study¹⁹ of fostamatinib disodium (FosD, R788; AstraZeneca, London, United Kingdom), an oral Syk SMI was evaluated in patients with recurrent B-NHL (N = 68; patients with DLBCL, FL, MCL, lymphoplasmacytic lymphoma, small lymphocytic lymphoma [SLL]/chronic lymphocytic lymphoma [CLL]). Maximum-tolerated dose of 200 mg twice per day was evaluated in phase II with objective response rates (ORRs) of 22% (DLBCL), 10% (FL), 55% (SLL/CLL), and 11% (MCL) and median progression-free survival of 4.2 months.¹⁹ Disruption of aberrant BCR signaling by Syk inhibition seems viable; however, FosD also inhibits Flt3 and Ret receptor

Table 2. Novel Small-Molecule Targeted Agents for B-NHL

Hallmark	Target	Therapy	NHL Type	Response (%)	Adverse Event	Reference No.
Proliferation	Syk	Fostamatinib disodium	DLBCL, FL, MCL, LPL (N = 68)	DLBCL, 22; FL, 10; MCL, 11	Neutropenia	19
	<i>Btk</i>	PCI-32765	DLBCL, FL, MCL, MZL (N = 47)	PFS, 4.2 months DLBCL, 17; FL, 27	Thrombocytopenia, diarrhea Allergic hypersensitivity	20
	PKC β	Enzastaurin	DLBCL (N = 55)	MCL, 75; MZL, 33 FFP, 22 (two cycles)	Neutropenia Hypomagnesemia, fatigue, edema, headache, motor neuropathy	21,22
	mTORC	Temsirolimus	B-NHL (N = 40)	FFP, 15 (four cycles) ORR, 40 (DLBCL, 14)	Thrombocytopenia Thrombocytopenia, rash, mucositis, hyperlipidemia, hyperglycemia, pneumonitis	23
			MCL (N = 35)	ORR, 33 (PFS, 6.9 months)		24
			MCL (N = 29)	ORR, 41 (one CR, 10 PR)		25
			MCL (N = 162)	ORR, 22		26
		Everolimus	DLBCL (n = 20); MCL (n = 14)	ORR, 32		27
		Deferolimus	MCL (N = 9)	PR, 30		28
Tumor suppression	HDAC	Vorinostat	DLBCL (N = 12)	RR, 25	Diarrhea, asthenia, thrombocytopenia, fatigue	29
			DLBCL (N = 18)	RR, 6		30
			MCL (N = 8)	No responses		31
	HDAC	Mocetinostat	DLBCL (N = 41)	RR, 15	Fatigue, myelosuppression, GI disturbance	32
Antiapoptosis	BCL2/BCL χ_L	ABT-263	B-NHL (N = 42)	DLBCL, NR	Thrombocytopenia	33
	BCL2/MCL-1	Obatoclax	B-NHL (N = 2)	one PR, one SD	CNS toxicity	34
	Survivin	YM155	B-NHL (N = 5)	two PR (DLBCL)	Stomatitis, pyrexia, nausea	35
Immune evasion	NK/T cell	Lenalidomide	B-NHL (N = 49)	ORR, 34 (DLBCL, 20)	Myelosuppression, asthenia	36
			B-NHL (N = 203)	ORR, 23 (DLBCL); ORR, 41 (MCL)		37,38
			MCL (N = 15)	ORR, 53 ORR		39
Stress response	Proteasome	Bortezomib	MCL (N = 155)	ORR, 33 (CR, 8)	Neuropathy, thrombocytopenia	40
			DLBCL (N = 12)	RR, 8		41
Limitless replication	CSK 2, 7, 9	SNS-032	B-NHL	NR	Mucositis, myelosuppression	42

Abbreviations: B-NHL, B-cell non-Hodgkin's lymphoma; Syk, spleen tyrosine kinase; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle-cell lymphoma; LPL, lymphoplasmacytic lymphoma; PFS, progression-free survival; *Btk*, Bruton's tyrosine kinase; MZL, marginal zone lymphoma; PKC β , protein kinase C beta; FFP, failure-free progression; mTORC, mammalian target of rapamycin complex; ORR, objective response rate; CR, complete response; PR, partial response; HDAC, histone deacetylase; NR, no response; SD, stable disease; NK, natural killer.

tyrosine kinases, and a formal kinase profile is not available. Nonmyelosuppressive combinations of FosD with rituximab (and/or SMIs to mTORC or proteasome) are likely to be active.

***Btk* inhibitor PCI-32765.** PCI-32765 (Pharmacyclics, Sunnyvale, CA) is an oral irreversible *Btk* SMI that binds to and inhibits the growth of malignant B cells overexpressing *Btk*. A phase I study²⁰ evaluated PCI-32765 in patients with relapsed or refractory B-NHL (N = 47), including patients with CLL and Waldenström macroglobulinemia. Five dose levels (1.25, 2.5, 5.0, 8.3, and 12.5 mg/kg per day) with a regimen of 4 weeks on/1 week off and a continuous daily dosing regimen of 8.3 mg/kg per day were explored. Pharmacokinetic and pharmacodynamic data demonstrated that PCI-32765 fully occupied the *Btk* active site in peripheral blood cells with minimal variability and fully inhibited surrogate biomarkers for up to 24 hours; it was well tolerated at 2.5 mg/kg or more per day. Of 35 patients who completed two cycles of therapy, 17 achieved complete response (CR) or partial response (PR). The RR was 82% for patients with CLL, 75% for those with MCL, 27% for those with FL, 33% for those with marginal zone lymphoma (MZL), and 17% for those with DLBCL, with an intent-to-treat ORR of 43%. In the first five dose groups (n = 40), there was

no evidence of a dose response, and duration of response was not determined. However, two patients from the first cohort received the dose for more than 12 months.²⁰

***PKC β* inhibitor enzastaurin.** PKC β identified by gene expression profiling is an unfavorable prognostic marker in DLBCL¹⁸ and MCL.²¹ It is a serine (Ser)/threonine (Thr) kinase important to signaling via BCR, NF- κ B, and VEGF.⁴⁴ Enzastaurin (Eli Lilly, Louvain, Belgium) is an oral Ser/Thr kinase SMI that blocks signaling via the PKC β /phosphoinositide 3-kinase (PI3K)/Akt pathway leading to enhanced apoptosis, decreased proliferation, and suppression of angiogenesis. In a phase II study,²² enzastaurin (500 mg once daily) was evaluated in patients with relapsed or refractory DLBCL (N = 55). Twelve (22%) of 55 patients experienced failure-free progression (FFP) for two cycles, and eight (15%) remained failure free for four cycles. Four patients (7%), including three who achieved CR and one with stable disease, continued to experience FFP for more than 20 to more than 50 months. Enzastaurin benefited a small subset of patients with DLBCL with prolonged FFP.²² Another phase II study²¹ evaluated enzastaurin (500 mg once daily) in patients with relapsed or refractory MCL (N = 60). Single-agent activity was absent, but 22

Fig 1. Targets and therapies for B-cell non-Hodgkin's lymphoma (B-NHL) within the context of the 10 hallmarks of cancer and overlapping oncogenic signaling pathways. (A) B-cell antigen receptor (BCR) composed of membrane immunoglobulin and associated Ig α /Ig β (CD79a/CD79b) when bound to antigen (Ag) leads to BCR aggregation, while the α - β heterodimer transduces signals that rapidly activate Src family kinases Lyn (Blk and Fyn) and immediate downstream tyrosine kinases spleen tyrosine kinase (Syk) and Bruton's tyrosine kinase (Btk), initiating a complex signaling cascade involving multiple adaptors, protein kinases, phosphatases, GTPases, and transcription factors that result in distinct consequences, including differentiation, survival, apoptosis, proliferation, and tolerance. Negative feedback loops that regulate BCR signaling (Lyn/CD22/Shp-1 pathway, SHIP, Cbl, Dok-1, Dok-3, Fc γ RIIB1, PIR-B, and BCR internalization) are not included in figure. In aggressive B-NHL, uncontrolled activation and proliferation of B-cells resulting from chronic active BCR signaling have been targeted and include (1) Syk (fostamatinib), (2) Btk (PCI-32765), (3) protein kinase C beta (PKC β ; enzastaurin), and (4) mammalian target of rapamycin (mTOR; temsirolimus, everolimus, deferolimus), highlighted in green with red inhibitor sign. Therapeutic targets in orange with red inhibitor sign with question mark are targets in B-NHL for which drugs are or may be available for evaluation in clinical trials. The aberrantly activated nuclear factor kappa B (NF- κ B) pathway has been targeted by overwhelming stress response by inhibiting (5) proteasome (bortezomib). Insensitivity to growth inhibitory signaling by epigenetic modulation has been evaluated by blocking (6) histone deacetylase (vorinostat, mocetinostat). Targeting other epigenetic enzymes such as DNA methyltransferase (DNMT) is of interest, particularly as combinations. Agents promoting apoptosis (7) BCL2/BCL $_L$ (ABT263) have entered clinical trials with promising activity. (B) Limitless replicative potential can be halted by inhibiting cell-cycle kinases (8) G1-S-G2 phase (cyclin-dependent kinases, checkpoint kinases) and (9) M phase (Aurora A/B). (C) Key hallmarks in the extracellular-stromal compartment critical for targeted therapies include (10) immune evasion (lenalidomide; inhibits T regulatory cells [Tregs]), invasion, and metastasis; neo-angiogenesis (bevacizumab, vascular endothelial growth factor receptor/platelet-derived growth factor receptor tyrosine kinase inhibitors); cytokines (AMD3100); and tumor-stroma interactions. BCAP, B-cell adaptor for phosphatidylinositol 3-kinase; PI3K, phosphoinositide 3-kinase; PLC γ 2, phospholipase C gamma 2; BLNK, B-cell linker; GRB2, growth factor receptor-bound protein 2; LAB, linker of activated B cells; SOS, son of sevenless; CARMA1, Caspase recruitment domain-containing membrane-associated guanylate kinase protein 1; MALT, mucosa-associated lymphoid tissue; IKK, I κ B kinase; TSC2, tuberous sclerosis protein 2; Me, methyl; His, histone; HDAC, histone deacetylase acetylation.

patients (37%) achieved FFP for three or more cycles; six of 22 patients maintained FFP for more than 6 months.²¹ Enzastaurin is under evaluation (v R-CHOP) in first-line and maintenance therapy after R-CHOP in DLBCL.³

mTORC inhibitors. mTOR Ser/Thr kinase complexes 1 (mTORC1) and 2 (mTORC2) regulate translation of key proteins positioned at the nodal points of several pathways during cell growth and proliferation. They are downstream effectors of PI3K/Akt and key regulators of translational initiation by phosphorylation of p70 S6 kinase and 4E binding protein-1. Targeting of mTORC in B-NHL is significant, and several small-molecule rapalogs based on the prototype rapamycin (temsirolimus [Wyeth, Madison, NJ], everolimus [Novartis, Basel, Switzerland], deforolimus [Merck, Whitehouse Station, NJ]) with less immunosuppression have been evaluated. One phase II study²³ evaluated temsirolimus in patients with treatment-refractory B-NHL (N = 40), with an ORR of approximately 40% in FL, CLL/SLL, and DLBCL and an RR of approximately 14% in DLBCL. Three patients with FL achieved CR.²³ In patients with treatment-refractory MCL (n = 35), treatment with temsirolimus resulted in an ORR of 38% (one CR, 12 PR) and a duration of response of 6.9 months.²⁴ Another study²⁵ of MCL (N = 29) evaluated a less myelosuppressive dose (25 mg weekly), with an ORR of 41% (one CR, 10 PR). A phase III study²⁶ of MCL (N = 162) comparing temsirolimus with physician choice demonstrated ORRs of 22% and 2%, respectively, with a 3-month survival advantage. A phase II study of temsirolimus plus rituximab in MCL is ongoing. A phase II study²⁷ evaluating everolimus in aggressive B-NHL (20 patients with DLBCL, 14 with MCL) showed a 32% ORR. An evaluation of deforolimus in patients with hematologic malignancies (N = 55) showed three of nine patients with MCL achieving PR.²⁸ mTORC SMIs are active in B-NHL, but resistance develops because of interference of a negative feedback loop that normally turns off this pathway. In malignancy, blocking of mTORC interferes with this inhibitory feedback loop, resulting in paradoxical enhanced PI3K/Akt signaling. Resistance may be overcome with a dual PI3K/mTORC SMI or combination of an mTORC SMI with a PI3K, Syk, or Btk SMI.

2. Enhancing Tumor Suppressor Activity

A program of gene silencing of tumor suppressors by epigenetic modification of DNA and/or histones is established in human malignancies. Several enzymes that epigenetically modify the nucleosome have been validated as anticancer targets; of these, DNA methyltransferase (DNMT) and histone deacetylase (HDAC) have resulted in approved drugs for hematologic malignancies.⁴⁵

HDAC inhibitors. The reversible acetylation of histones catalyzed by histone acetyltransferases and HDACs within the nucleosome structure modulates DNA repair and gene expression. In tumors, HDACs drive the equilibrium of this reaction in favor of deacetylation and tightening of histones, leading to epigenetic silencing.⁴⁵ DNA methylation and histone deacetylation work in concert in gene silencing as a result of direct binding interactions between DNMTs and HDACs. HDAC inhibitors (targeting class I and II but not class III) induce cell-cycle arrest, promote differentiation, and hyperacetylate BCL6 (transcriptional repressor)⁴⁶ and HSP90 and its client proteins. The latter effect seems to achieve a disruption of BCL6 and HSP90 function similar to that produced by HSP90 inhibitors.⁴⁵

Vorinostat (Merck), an oral pan-HDAC inhibitor approved for cutaneous T-cell lymphoma, has been evaluated in aggressive B-NHL.

Among 12 patients with DLBCL, three responses were observed (one CR, two PR).²⁹ In a second study³⁰ of patients with relapsed DLBCL (N = 18) treated at 300 mg twice per day (2 weeks/3 weeks or 3 days/1 week), only one patient achieved CR. In a third study³¹ (N = 27; patients with FL, MZL, MCL), no responses were seen in MCL (n = 8), whereas activity was seen in FL (six CR, four PR). MGCD0103 (mocetinostat; MethylGene, Montreal, Quebec, Canada), an oral class I HDAC inhibitor, was evaluated in a phase II study³² of patients with relapsed or refractory DLBCL (n = 41) and FL (n = 28). Among patients with DLBCL, a 15% RR (one CR, five PR) was observed, and of the evaluable patients, 60% had tumor reduction by RECIST (Response Evaluation Criteria in Solid Tumors). Other HDAC inhibitors in early phase clinical trials in B-NHL are romidepsin (Gloucester Pharmaceuticals, Summit, NJ), panabinstat (Novartis), and belinostat (CuraGen, Branford, CT).^{47,48} Because of modest single-agent activity, combination studies have been initiated with DNMT inhibitors (eg, Vidaza [azacitidine; Celgene, Summit, NJ]), and bortezomib.^{47,48}

3. Targeting Antiapoptosis

Balanced processes of cell division and programmed cell death maintain cellular homeostasis. Extrinsic (tumor necrosis factor family of death receptors) and intrinsic (BCL2 family) apoptosis-promoting signaling pathways play a pivotal role in malignant progression and response to therapy. Therapeutic targeting of dysregulated antiapoptosis and autophagy provides a rationale to develop agents that promote NHL apoptosis.

BCL2/MCL1 inhibitors. Malignant cells highjack the BCL2 family of 25 pro- and antiapoptotic proteins to primarily inhibit apoptosis by overexpression of antiapoptotic members and sequestration and gene deletion of proapoptotic members.⁴⁵ In most FL and in some DLBCL (17%) cases, BCL2 is juxtaposed with the Ig heavy-chain locus, resulting in a t(14;18) translocation, aberrant overexpression, and resistance to apoptosis.⁴⁹ ABT-263, a BH3-mimetic oral SMI of BCL2, BCLX_L, and BCLW, binds with high affinity and inhibits BCL2 family proteins. A phase I study evaluated ABT-263 in patients with relapsed or refractory NHL (n = 42) at doses of 10, 20, 40, 80, 160, 225, and 315 mg in a 21-day cycle with a schedule of 14 days on/7 days off. PR was observed in CLL (n = 2) and natural killer/T-NHL (n = 1), and minor responses were observed in FL (n = 4).³³ Because ABT-263 has no activity against MCL1, drug resistance may be overcome in phase II combination studies with rituximab, bortezomib, or HDAC inhibitors. Another approach to overcoming drug resistance utilizes the broad-spectrum BCL2/MCL1 SMI obatoclax (GeminX, Malvern, PA), which was evaluated in two studies of weekly 1-hour (GX001; n = 8) and 3-hour infusions (GX008; n = 27) in patients with refractory solid tumors or NHL, respectively. While receiving GX005, one patient with NHL achieved PR for 2 months, and another patient with NHL maintained stable disease for 18 months.³⁴ In a third study,⁵⁰ (CRU).

Blocking inhibitors of apoptosis. Survivin, a member of the inhibitor of apoptosis family, functions to inhibit caspase activation in a cell cycle-dependent manner and negatively regulates apoptosis. YM155 (Astellas Pharma, Tokyo, Japan) is an SMI of survivin that resulted in three of five patients with NHL achieving PR, two of whom had DLBCL.³⁵ Other agents targeting apoptosis include antisense oligonucleotides targeting X-linked inhibitor of apoptosis, a potential therapy for B-NHL.

4. Inhibiting Limitless Replication

The ability of tumor cells to possess limitless replication potential is linked to maintenance of telomeric DNA (repetitive TTAGGG sequences), located on the ends of chromosomes. GC B-NHLs have long telomeres, implying minimal telomere erosion during lymphomagenesis, whereas GC-inexperienced NHLs have short telomeres and are good candidates for treatment with reverse transcriptase telomerase SMIs,⁵¹ currently in early phase studies. Aberrant cell-cycle proliferation of tumor cells is driven by overexpression of cyclin-dependent kinases, checkpoint kinases, and mitotic kinases (Aurora) with abnormal DNA damage repair responses (poly[ADP-ribose] polymerase). SMIs targeting cell-cycle kinases and poly(ADP-ribose) polymerase have entered clinical trials; SNS-032, a cyclin-dependent kinase 2, 7 and 9 inhibitor, was the first to be evaluated in refractory solid tumors or lymphomas.⁴² No single-agent activity has been reported.

5. Blocking Neoangiogenesis

NHLs grow and metastasize as a result of neoangiogenesis development. VEGF and its receptors have been targeted with biologic therapies alone or with R-CHOP in DLBCL.³ Several SMIs targeting VEGF receptor, *PDGFR*, and fibroblast growth factor receptor tyrosine kinases key to angiogenesis have been evaluated in solid tumors but not in NHL.⁴⁵

6. Inhibitors of Invasion and Metastasis

Malignant lymphoid cells have acquired genetic programs that promote migration, extravasation, homing, and metastasis by dysregulated expression of five classes of cell adhesion molecules: integrins, cadherins, Ig-like cell adhesion molecules, selectins, and CD44s. Cell adhesion-mediated survival pathways amenable to SMI therapy include follicle adhesion kinase, integrin-linked kinase, Src, PI3K/Akt, Ras/Raf, Mek/Erk, PKC, NF- κ B,⁴⁵ and transforming growth factor beta (TGF β). No specific trials are ongoing for NHL, but bortezomib, a proteasome SMI that indirectly targets the NF- κ B pathway, has been evaluated in NHL.

7. Targeting Immune Evasion

In B- and T-NHL, there is an abundant infiltrate of innate immune cells (macrophages, mast cells, neutrophils, T-regulatory cells [Tregs]) that correlate with increased immune evasion, neoangiogenesis, and poor prognosis. In contrast, an abundance of infiltrating cytotoxic T-cells correlates with favorable prognosis. Tregs are CD4+CD25+FOXP3+, but different subtypes exist. In vivo depletion of Tregs using antibodies to CD25 or denileukin diffitox (Ontak; Eisai, Woodcliff Lake, NJ) enhances antitumor T-cell responses and induces regression of experimental tumors.⁴ Therefore, targeting defective immunity in B-NHL is an active area of research that has included vaccine-based approaches.⁴⁵

Immunomodulating agents. Lenalidomide (Celgene), the most advanced immunomodulating agent in NHL development, has a multitude of antilymphoma actions, including activation of natural killer/T-cells, upregulation of costimulatory molecules (CD40, CD80, CD86) and Fas ligand CD95, inhibition of angiogenesis, abrogation of proinflammatory cytokine production, and modulation of adhesive events within the tumor microenvironment.⁵² In a phase II study³⁶ evaluating lenalidomide (25 mg once daily for 21 days, every 4 weeks) in aggressive B-NHL (N = 49), an ORR of 34% was reported, with an

RR of 20% among the 26 patients with DLBCL (one CR, two CRu). Median duration of response was 6.2 months, and progression-free survival was 4 months. Major adverse events were myelosuppression and asthenia. The phase II NHL-003 trial of lenalidomide is ongoing (N = 203) in patients with aggressive NHL who have undergone one prior treatment. Interim analysis of 73 patients with DLBCL showed an ORR of 29% (three CR, 18 PR),³⁷ and 39 patients with MCL had a 41% ORR (13% CR/CRu, 28% PR).³⁸ In refractory MCL (n = 15), an ORR of 53%, with a 20% CR, was observed with lenalidomide at 25 mg once daily, days 1 to 21, every 28 days for up to 52 weeks.³⁹ A phase I combination study⁵³ of lenalidomide (5 to 25 mg) with rituximab was explored in patients with refractory MCL (N = 15). No responses were observed in the 10- and 15-mg cohorts, but at the maximum-tolerated dose (20 mg), five of six patients experienced response, including one CR. CALGB (Cancer and Leukemia Group B) is conducting a phase II combination study of lenalidomide plus bortezomib in treatment-resistant MCL. Nonmyelosuppressive mechanism of action-based therapies (eg, Syk, *Btk*, or PI3K/mTOR SMIs) are likely to be successful in combination with lenalidomide.

8. Overwhelming the Stress Response

The stress response phenotype composed of metabolic (lactic acidosis), proteotoxic (heat shock response), mitotic (chromosome instability), oxidative (reactive oxygen species), and DNA damage (double-strand breaks) can be exploited to sensitize and/or overload NHL cells to propel them beyond a point of no return.¹⁶ Also, cells with defective apoptosis survive metabolic stress by using autophagy.⁴⁵

Inhibitors of the proteasome. Abnormally folded intracellular proteins (> 80%) are proteolyzed by the ubiquitin-proteasome pathway, a multicatalytic protease complex that possesses three enzyme functions (trypsin-like, chymotrypsin-like, caspase-like).⁵⁴ Bortezomib (Millennium Pharmaceuticals, Cambridge, MA), a reversible dipeptidyl boronic acid derivative, has been approved by the US Food and Drug Administration for MCL. Bortezomib inhibits the degradation of I κ B α and downregulates NF- κ B, leading to reversal of chemoresistance and/or increasing chemotherapy sensitivity.⁴⁵ Studies have demonstrated the important role of the NF- κ B pathway in aggressive NHL, including MCL,⁵⁵ ABC-type DLBCL,^{7,43,56} and PTCL.^{12,13} A phase II study⁴⁰ of bortezomib (1.3 mg/m² on days 1, 4, 8, and 11 of a 21-day cycle) in patients with refractory MCL (N = 155) showed an ORR of 33% (n = 144), 8% of which represented patients achieving CR, with a duration of response of 15.4 months. In contrast, in refractory DLBCL, bortezomib administered at 1.5 mg/m² on days 1, 4, 8, and 11 every 21 days for six cycles resulted in modest activity (one in 12 patients achieved CR).⁴¹ In a randomized phase II study⁵⁷ in which bortezomib (4 days v 2 days per cycle) was added to R-CHOP in newly diagnosed patients with B-NHL (N = 49; including patients with DLBCL, MCL, FL, MZL, SLL), 84% of patients achieved CR/CRu (MCL, 100%; DLBCL, 94%). A second phase II study⁵⁸ of bortezomib plus R-CHOP in DLBCL (N = 40) demonstrated an RR of 88%. However, the percentage of patients with ABC DLBCL was not disclosed. To decrease neuropathy, vincristine was dropped from R-CHOP in a trial involving newly diagnosed patients with DLBCL. Attenuated dose of bortezomib with standard-dose vincristine may be a possible approach that does not compromise efficacy. A phase I/II study⁵⁹ of bortezomib versus bortezomib plus dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone in patients with aggressive DLBCL for whom R-CHOP failed showed an

Table 3. Novel Small-Molecule Targeted Agents for PTCL

Hallmark	Target	Therapy	Dose/Schedule	Response (%)	Adverse Events	Reference No.
Proliferation	RFC-1, FPGS	Pralaterxate (folotyn)	30 mg/m ² IV, once weekly for 6 weeks every 7 weeks (N = 111)	ORR, 28 (CR, 9; PR, 18); MDR, 9.4 months	Mucositis, nausea, fatigue, thrombocytopenia	63
Tumor suppression	HDAC	Romidepsin	14 mg/m ² IV days 1, 8, 15 every 4 weeks (N = 48)	ORR, 31 (CR, 8; PR, 23); MDR, 9.0 months	Infection, sepsis, pyrexia, myelosuppression, arrhythmia	64
Immune evasion	NK/T cell	Lenalidomide	25 mg once daily, days 1 to 21, 28-day cycle (N = 24)	ORR, 30; PFS, 96 days; OS, 241 days	Myelosuppression, asthenia	65

Abbreviations: PTCL, peripheral T-cell lymphoma; RFC-1, reduced folate carrier-1; FPGS, folypolyglutamate synthase; IV, intravenously; ORR, objective response rate; CR, complete response; PR, partial response; MDR, median duration of response; HDAC, histone deacetylase; NK, natural killer; OS, overall survival.

ORR of 83% for ABC type versus 13% for GC type, with a longer survival of 10.8 months versus 3.4 months, respectively. This study essentially tested adding etoposide to bortezomib. A better study would be bortezomib plus rituximab plus etoposide, cytarabine, cisplatin, and methylprednisolone. SWOG (Southwest Oncology Group) is conducting a randomized study of R-CHOP plus bortezomib versus R-CHOP in patients with newly diagnosed MCL. Carfilzomib, an irreversible proteasome inhibitor, and NEDD8 activating enzyme SMI (MLN4924) are novel blockers of the ubiquitin-proteasome pathway entering early phase studies.⁴⁵

9. Abrogating Stromal Subversion

Targeting the microenvironment in the genetic context of NHL subtypes is a potentially useful approach to therapy.¹⁷ Growth factors generating malignant stromal response that promotes fibrosis and an invasive phenotype with associated drug resistance have been identified (eg, Sonic hedgehog, TGF β , hepatocyte growth factor, fibroblast growth factor, PDGF, VEGF, Wnt, Notch).¹⁷ In stromal-1, secreted protein acidic and rich in cysteine and CTGF can be targeted with abraxane and anti-CTGF Mab, respectively.⁴³ In stromal-2, VEGF, tyrosine kinase endothelial, and CXCR4 may be targeted with bevacizumab, Tie-2 inhibitors, and CXCR4 SMIs, respectively.⁴³

10. Manipulating the Serum Cytokine Response

Immune-derived cytokines, chemokines, and proangiogenic proteins (eg, CXCL12 [SDF-1], interleukin-1, interleukin-6, TNF α , TGF β) are known tumor promoters.⁴⁵ Rationale for inhibiting the activity of cytokines is to enhance the anti-NHL activity of immune

effector cells and direct anti-NHL activity.⁴⁸ The CXCR4-CXCL12 axis is widely expressed on many tumor types and involved in cell migration, cell invasion, and maintenance of tumor cells in close contact with the stroma.⁶⁰ Three CXCR4 antagonists are in clinical development. The CXCR4 SMI AMD3100 (plerixafor; Genzyme, Cambridge, MA) is approved for stem-cell mobilization before autologous stem-cell transplantation in hematologic malignancies.⁶¹ MDX-1338 (Medarex, Princeton, NJ) is a Mab to CXCR4, and BKT140 (Biokine Therapeutics, Jerusalem, Israel) is a CXCR4 antagonist⁶²; they warrant combination with R-CHOP in aggressive B-NHL.

Targets and therapies for PTCL. In PTCL, we identified a therapeutic signature (eg, Aurora A, Nek2, c-MET, Syk, α -PDGFR, Lck, Lyn, CXCR4, NF- κ B2) amenable to SMI therapy.¹² SMIs active in PTCL include folate analog pralaterxate,⁶³ HDAC inhibitor (depsipeptide),⁶⁴ and lenalidomide⁶⁵ with modest single-agent activity (RR of approximately 30%; Table 3). Rarity of PTCL limits clinical trials with potentially active targeted agents (Aurora A, c-Met, Nek2, proteasome). Platinum- and gemcitabine-based combinations⁴ continue to be used, but adding targeted SMIs remains a challenge.⁶⁶

CONCLUSION

The opportunities for clinical research aimed at improving the cure rates of aggressive NHL have never been greater. We have moved from a paucity of interesting new agents to a plethora of exciting ones. The problem now is how best to develop these new agents. There are in fact

Table 4. Future Targeted SMIs for Aggressive B-NHL and PTCL

Hallmark	Target	Agent	Comments	Reference No.
Proliferation	<i>Btk</i>	AVL-292	Irreversible ATP-site SMI	Avila Therapeutics (Waltham, MA)
	BCL6	BCL6 SMI	BCL6 BTB domain binding groove SMI	67
Tumor suppressor	DNMT	Vidaza, decitabine	Epigenetic regulation	45
Antiapoptosis	NEDD8	MLN4924	UPP pathway	68
Stress response	HSP90	AT13389, XL888, NVP-AUY922	Phase I studies	69
Limitless replication	Aurora kinase	MLN8283	Phase II NHL ongoing	70
Neoangiogenesis	VEGFR, <i>PDGFR</i>	Vatalanib, pazopanib, ABT-869	Phase I studies	12,45
Invasion/metastasis	c-MET	Crizotinib, foretinib, amuvatinib	Phase I studies	12,45

Abbreviations: B-NHL, B-cell non-Hodgkin's lymphoma; PTCL, peripheral T-cell lymphoma; *Btk*, Bruton's tyrosine kinase; SMI, small-molecule inhibitor; BCL, B-cell lymphoma; DNMT, DNA methyltransferase; UPP, ubiquitin-proteasome pathway; VEGFR, vascular endothelial growth factor receptor; *PDGFR*, platelet-derived growth factor receptor.

many more agents and combinations of agents than available to patients enrolling onto early developmental treatment trials in aggressive lymphoma. The old paradigm of simply adding new agents to existing ones has been relatively nonproductive, aside from the major impact of rituximab. A hypothesis-driven method of clinical investigation is necessary. Priority should be given to agents for which strong scientific rationale exists based on targeting critical pathways or processes in lymphoma cells. Multiagent blockade of those pathways or functions will probably be required. Although it is theoretically possible that inactive agents will somehow miraculously synergize with other active agents, the history of that occurring is extremely limited. Although it may be argued that the situation may be different in some solid tumors, the recent combination of R-CHOP with a new antiangiogenic agent that lacked single-agent activity in DLBCL was not successful. In addition, the use of strong preclinical data in cells lines or mouse xenographs does not ensure subsequent clinical success, but it at least provides a signal of activity. It is hard to imagine that an agent or combination of agents that does not work in the cell lines of mice will work in humans. Finally, we need to increase the number of patients enrolling onto early developmental trials. This is especially important because recent scientific discovery has proven that there is significant heterogeneity in lymphoma, such as in DLBCL. It is imperative that sufficient numbers of patients are entered on trials so that the response of the critical subsets can be analyzed. There is good reason to hope that exciting new agents evaluated in sound mechanistic studies will increase physician and patient enthusiasm.

Sequencing the human genome promised a cornucopia of novel drugs; genetic targets previously unknown would succumb to pharmacologic intervention in an era of personalized medicine, in which treatment would be tailored to an individual's genetic makeup. Drug companies continue to focus on targets discovered before the new

technologies. Predictive and prognostic biomarkers (genes, proteins, novel imaging) are the rave, but they will be rendered obsolete once effective drugs become the norm, as was seen in infectious diseases. Several unexplored targeted agents are now available for evaluation in both B- and T-NHL (Table 4). A framework is being explored to evaluate targeted therapies within overlapping oncogenic pathways in the context of the 10 hallmarks of cancer.

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