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Emerging Treatment Options for Adolescents and Young Adults with Relapsed or Refractory Lymphoma

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Abstract

Lymphomas are amongst the most common cancers in Adolescents and Young Adults (AYA). Despite favorable outcomes with upfront therapy, survival in patients with relapsed or refractory disease remains poor. Promising therapeutic agents are emerging, including monoclonal antibodies, antibody drug conjugates, immune checkpoint inhibitors, cytotoxic T-cell therapies, small molecule pathway inhibitors and epigenetic modulators. Clinical trials of novel agents have predominantly enrolled older adult patients. Furthermore, research relating to the biology of lymphomas has focused predominately on younger children and older adults. Future investigation should concentrate on the biology of lymphomas in AYAs and improving their participation in clinical trials.

Introduction

Lymphoid malignancies are among the most common cancers in Adolescents and Young Adults (AYA), defined as 15-39 years [1,2]. Classical Hodgkin Lymphoma (HL), which is the most common hematologi malignancy in AYAs, accounts for up to 12% of cancers seen in patients aged 15-29 years [2]. Despite excellent outcomes with upfront therapy, a small proportion of patients will have primary refractory disease or experience relapse [3]. Salvage chemotherapy followed by high-dose chemotherapy with autologous stem cell transplant (ASCT) remains the standard of care but induces long-term remissions in only approximately 50% of patients [4].

Non-Hodgkin Lymphoma (NHL) represents a heterogeneous group of lymphoid malignancies of B, T and NK–cell origin often separated into aggressive e.g. diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), and anaplastic large cell lymphoma (ALCL); and indolent forms [5]. DLBCL predominates in AYA patients, comprising about 60% of NHL cases [2,6]. Gene expression profiling has revealed DLBCL can be classified into two major variants. The germinal center B-Cell (GCB) subtype which is more common in children and AYAs; and the less favorable activated B-cell (ABC) DLBCL mostly seen in older adults [7]. Similarly, salvage chemotherapy followed by ASCT is also the standard treatment for relapsed/refractory DLBCL [8]. As in HL, the inability to achieve a metabolic complete remission by functional imaging is associated with worse post-transplant outcomes irrespective of type of salvage regimen used [9-12] and patients who are transplant ineligible or have relapsed after transplant have very limited options. Options for patients with relapsed, indolent NHLs include novel drugs, such as lenalidomide and idelalisib; and as well, stem cell transplantation is considered for those who are resistant to rituximab and alkylating agents [13]. In addition, there is no consensus regarding optimal treatment for relapsed/refractory peripheral T-cell lymphoma (PTCL), which continues to be associated with a very poor prognosis [14]. These highlight the need to develop effective treatment strategies for relapsed and refractory lymphoma.

Here we review some of the emerging therapeutic options in patients who have failed front-line therapy, focusing on HL and DLBCL which are the most common lymphomas in AYAs.

AYA Lymphoma and Disease Biology

In general, improvement in overall survival in AYAs has lagged behind that of younger and older patients with cancers. While the reasons are not well understood, they likely include differences in adherence, care delivery and disease biology [15-17]. Whereas outcomes in younger children have been advanced through participation in cooperative group clinical trials, participation by adolescents in either pediatric or adult clinical trials remains low [18,19].

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Figure 1: Cellular targets of novel therapies in lymphomas.
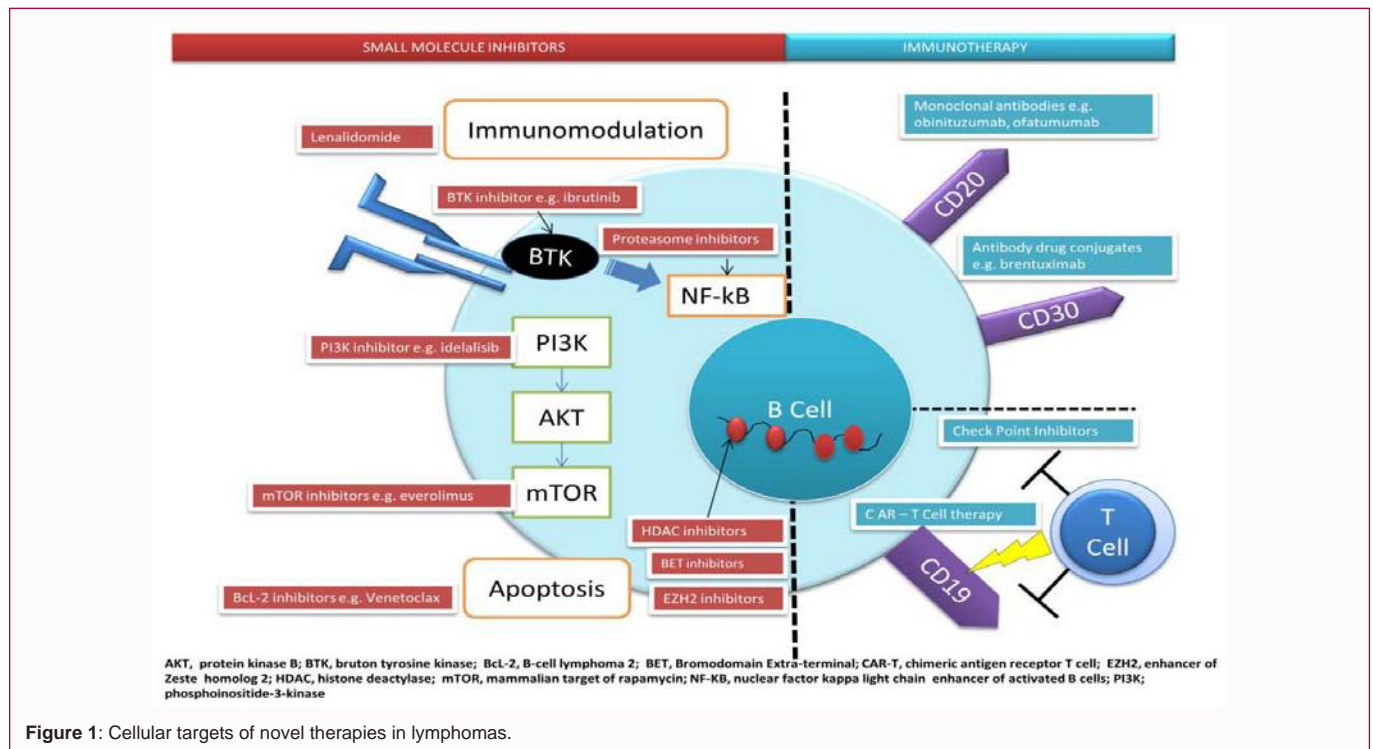
In recent years our understanding of lymphoma biology and the pathways that drive oncogenesis has evolved, leading to opportunities to explore novel targeted therapies. Some of these pathways and their targets are illustrated in Figure 1. Unfortunately, studying the biology of lymphomas in AYAs has not kept pace with our understanding of the disease in children and older adults. Hence, strategies for treating this population have not been clearly defined [2]. These novel agents have been tested in clinical trials, typically in older adult populations. We recognize that the young adults are underrepresented in many trials; particularly the B-NHL studies and differences in biology across age groups, likely inform treatment responses. Nonetheless, we feel the results of these studies may warrant extrapolation to adolescent and young adult populations.

Immunotherapy

Monoclonal antibodies targeting cell surface antigens

The emergence of the anti-CD20 monoclonal antibody (mAb) rituximab significantly improved outcomes in the first-line treatment of all CD20+ NHLs, particularly DLBCL and follicular lymphoma (FL) [20,21]. Targeting CD20 should have similar efficacy in B-cell lymphomas in AYAs. While multiple studies of adult B-NHL demonstrated efficacy of rituximab, the experience in pediatrics lagged behind, perhaps due to historically good outcomes in children and adolescents. The Intergroup Trial for children and adolescents with B-NHL (ANHL1131), a randomized phase 3 study, compared the current chemotherapy backbone (LMB96) with LMB96 chemotherapy plus rituximab in patients with high risk B-NHL. The results of this study have not been published, but interim analysis showed superior 1-year EFS in the rituximab arm (94.2% *vs.* 81.5% in the non-rituximab arm). Hence, the current recommendation for treating newly diagnosed B-NHL in pediatrics is rituximab plus chemotherapy.

Despite the successes with rituximab, the development of rituximab-refractory disease led to the development of other anti-CD20 mAbs which may have improved efficacy [22]. Ofatumumab and obinutuzumab represent newer generation anti-CD20 mAbs which have shown clinical activity in relapsed/refractory NHLs. Obinutuzumab (GA101) is the first humanized type II glycoengineered anti-CD20 mAb. It has a low level of complement-dependent cytotoxicity and increased direct non-apoptotic cell death, compared to rituximab based on *in vitro* and *in vivo* studies [22]. Used as a single agent in both relapsed/refractory indolent and aggressive B-NHLs, obinutuzumab resulted in objective response rates (ORR) of 55% and 28% respectively, with a median progression free survival (PFS) of 11.9 months in the indolent NHL cohort [23,24]. The median age of patients in that study was 71 years (range 22-85 years). Improved response rates of 93 to 96% were observed when this agent was added to a chemotherapy backbone in patients with relapsed/refractory FL [25]. The drug is currently being evaluated in combination with other agents in ongoing clinical trials in both the relapsed and upfront settings.

Of atumumab is a fully humanized second generation type I anti-CD20 mAb. Preclinical data suggested it had improved complement-dependent cytotoxicity compared with rituximab [26] and superior activity against both rituximab-sensitive and resistant cell lines [27]. Coiffier et al. [28,29] first reported ORR of 44% in relapsed/refractory Chronic Lymphocytic Leukemia (CLL) patients, which led it to its regulatory approval for this indication. However it is yet to demonstrate any clinical activity in relapsed/refractory DLBCL [30].

Monoclonal antibodies targeting other B-cell surface antigens have also been developed, although these have not been approved for use in the United States. One of such is epratuzumab, a humanized mAb against CD22, which is expressed by most NHLs. Combined with the radioisotope Yitrium[90] in a phase 1 study of adults with relapsed/refractory aggressive NHL, ORR of 53% was observed. This included response rates of 50% in the DLBCL group, and responses in all four evaluable patients in the transformed FL group [31]. MEDI-551 an anti-CD19 monoclonal antibody also demonstrated single-

Table 1: Novel immunotherapy agents in clinical investigation for relapsed/refractory lymphomas.

Agent	Target	Author	Disease subtypes	Number treated (N)	Response (%)	PFS/DOR (months)	Common toxicities (%)
Monoclonal Antibodies							
Obinutuzumab	CD20	Morschauser [23]	DLBCL, MCL	42	ORR 30	Median DOR (9.8)	Grade 1 or 2 infusion reactions (>70)
Antibody Conjugates							
Brentuximab vedotin	CD30	Younes [4]	HL	102	ORR 75, CR 34	Median DOR(20.5)	Neuropathy (42), fatigue (34) neutropenia (19)
	CD30	Pro [37]	ALCL	58	ORR 86, CR 57	Median DOR (13.2)	Neutropenia (21), thrombocytopenia (14) neuropathy (12)
Polatuzumab vedotin	CD79b	Palance-Wessels [41]	DLBCL, FL, MCL	45	ORR 55	Median DOR (6.2)	Grade 3/4 neutropenia (40), anemia (11), neuropathy (9)
Immune Check Point Blockade							
Nivolumab	PD-1 receptor	Ansell [46]	HL	23	ORR 87, CR 17	PFS at 24 weeks 86%	Rash (22) and Grade 3 AEs (22)- pancreatitis, pneumonitis, colitis, MDS
Nivolumab	PD-1 receptor	Younes [47]	HL	80	ORR 66	NA	Fatigue (25), infusion reaction (20), rash (16)
Pembrolizumab	PD-1 receptor	Armand [48]	HL	31	ORR 65, CR 16	PFS at 24 weeks 69%	Hypothyroidism (10), Pneumonitis (10)
Bispecific T-cell Engagers							
Blinatumomab	CD3/19	Goebeler [68]	NHL	76	ORR 69 (55 DLBCL)	Median DOR (13.5)	Fever(86) fatigue (55), constipation (36), headaches (36), tremor(36)
CAR T-Cell therapy							
Anti CD19 CAR T	CD19	Kochenderfer [59]	B-NHL	15	ORR 92, CR 61.5	DOR (9-22)	Fever, hypotension, neurologic toxicity

ALCL: Anaplastic Large Cell Lymphoma; B-NHL: B cell Non Hodgkin Lymphoma; CR: Complete Response; DOR: Duration of response; DLBCL: Diffuse Large B-cell Lymphoma; FL: Follicular Lymphoma; HL: Hodgkin Lymphoma; MCL: Mantle Cell Lymphoma; ORR: Overall response rate; PTCL: Peripheral T-Cell Lymphoma; PFS: Progression Free Survival

agent activity in a cohort that included both relapsed/refractory FL and DLBCL patients (ORR 24%) [32].

Antibody-Drug conjugates

Antibody–drug conjugates (ADCs) consist of anti-cancer agents covalently linked to monoclonal antibodies directed at antigens which are differentially over expressed in tumor cells. Brentuximab vedotin (SGN-35) is a CD30-directed antibody conjugated to the anti-microtubule monomethyl auristatin E (MMAE). CD30, a trans-membrane glycoprotein is expressed on the Reed Stenberg cells in HL and on ALCL cells [33]. Younes et al. [4] observed 75% ORR and a 34% Complete Response (CR) in 102 heavily pre-treated patients (median age 31 years) with relapsed/refractory HL. The median duration of response (DOR) was 20.5 months in those who achieved a CR. Following these results; several other studies have demonstrated similar and durable responses in relapsed/refractory HL [34-36]. Brentuximab also showed remarkable activity in relapsed/refractory ALCL (ORR 86%, CR 57%) [37].

The Food and Drug Administration (FDA) has approved brentuximab for treatment of patients with refractory HL post-ASCT, transplant ineligible HL patients after failure of at least two prior multi-agent chemotherapy regimens, and relapsed/refractory ALCL after failure of at least one prior multi-agent chemotherapy regimen. Brentuximab has also been used successfully as a bridge to transplant in refractory HL patients [34]. Combined with the alkylator bendamustine in pre-ASCT patients with relapsed or refractory HL, ORR of 93% with a CR of 76% was observed and majority of these patients proceeded to ASCT (at 18 months, PFS of 75%) [38]. Although some activity was observed in CD30+ NHL [39], its role in B-NHL has not been established. The drug is generally well

tolerated. The most common reported adverse events are neuropathy, predominantly sensory, and hematologic toxicities [40].

Polatuzumab vedotin consists of an anti-CD79b monoclonal antibody, and like brentuximab is conjugated to MMAE. A phase 1 study of single-agent polatuzumab vedotin in patients with relapsed/refractory NHL showed ORR of 55% in 42 evaluable patients. In addition, 7 out of 9 patients treated with both polatuzumab and rituximab had an objective response [41]. Similar to brentuximab, the most common adverse events have been neutropenia, anemia and peripheral sensory neuropathy [41]. Phase 2 studies of polatuzumab in combination with other agents - NCT02611323 and NCT02600897; are currently active and enrolling patients. Denintuzumab mafodotin (SGN-CD19A), an anti-CD19 antibody conjugated to monomethyl auristatin F (MMAF), a second generation microtubule inhibitor, is also being evaluated in phase 1/2 trials for relapsed/refractory NHL.

Immune check point inhibitors

Recent evidence has demonstrated a variety of tumors are able to evade the host immune system through immune check point pathways such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed-death 1 (PD-1) [42]. Initial preclinical and clinical benefits of check point blockade were first demonstrated in melanoma [43,44] Subsequent data in HL demonstrating PD-1 related immune evasion by Reed-Sternberg cells have led to early phase studies of PD-1 inhibitors in this disease [45]. Ansell et al. [46] reported ORR of 87%, PFS of 86% at 24 weeks, following single agent PD-1 blockade with nivolumab in 23 heavily pre-treated relapsed/refractory HL patients. Also, Younes et al. [47] recently published results of their ongoing single-arm phase 2 study of nivolumab in adult patients with recurrent HL who had failed both ASCT and

Table 2: Novel small molecule inhibitors in clinical investigation for relapsed/refractory lymphomas.

Agent	Target	Author	Disease subtypes	Number treated (N)	Response (%)	PFS/DOR (months)	Common toxicities (%)
Histone Deacetylase Inhibitors							
Romidepsin	HDAC	Coiffier [87]	PTCL	130	ORR 25, CR 15	Median DOR (28)	Thrombocytopenia (24), neutropenia (20), infections (19)
Belinostat	HDAC	O'Connor [88]	PTCL	129	ORR 25.8, CR 10.8	Median DOR (13.6)	Anemia (10), thrombocytopenia (7), neutropenia and dyspnea (6)
Pabinostat	HDAC	Younes [83]	HL	129	ORR 27, CR 4	Median DOR (6.9)	Thrombocytopenia (79) anemia (21), neutropenia (21)
Vorinostat	HDAC	Ogura [107]	FL	39	ORR 49	Median PFS (20)	Thrombocytopenia (48) neutropenia (41)
Immunomodulatory agents							
Lenalidomide	Multiple	Witziq [70]	DLBCL, FL, MCL	217	ORR 35, CR 13	Median DOR (10.6)	Neutropenia (41), thrombocytopenia (19), anemia (9.2)
Combination therapies							
Bendamustine/Rituximab	Cytotoxic/CD20	Ohmachi [108]	DLBCL	59	ORR 62.7, CR 37.3	Median PFS (6.7)	Lymphopenia (78), neutropenia (76), thrombocytopenia (20)
Panobinostat/Bortezomib	HDAC/Proteasome	Tan et al. [109]	PTCL	25	ORR 43, CR 21.7	NR	Thrombocytopenia (68), neutropenia (40), diarrhea (20)
CUDC-907	HDAC/PI3K	Younes et al. [93]	Multiple	44 (9 DLBCL)	ORR 55 for DLBCL	NR	Thrombocytopenia (20), neutropenia (7), hyperglycemia (7)

B-NHL: B cell Non Hodgkin Lymphoma; CR: Complete Response; DOR: Duration of response; DLBCL: Diffuse Large B-cell Lymphoma; FL: Follicular Lymphoma; HDAC: Histone Deacetylase; HL: Hodgkin Lymphoma; MCL: Mantle Cell Lymphoma; ORR: Overall response rate; PI3K: Phosphatidylinositol 3-Kinase; PTCL: Peripheral T-Cell Lymphoma; PFS: Progression Free Survival; TTP: Time To Progression

brentuximab. They reported ORR of 66% among their cohort of 80 patients (age range 28-48 years, median 37 years), which was identical to findings observed by Armand et al. [48] in the phase 1 study of pembrolizumab in relapsed/refractory HL patients after brentuximab failure (ORR 66%, CR 16%, PFS 69% at 24 weeks and 46% at 52 weeks). These findings recently led to the accelerated FDA approval of nivolumab for patients with recurrent HL.

PD-1 appears to be important in the biology of subsets of NHL, including Epstein Barr Virus (EBV) - associated lymphomas. In a study of nivolumab, ORR of 36% and 40% were also reported in DLBCL and FL respectively [49]. An earlier phase 1 study of the CTLA-4 inhibitor, Ipilimumab had not demonstrated any significant activity in NHL [50]. In patients with relapsed FL, PD-1 inhibitor pidilizumab in combination with rituximab resulted in ORR of 66% (CR 52%), [51] supporting a role for check point blockade in relapsed/refractory NHL. In parallel with on-going investigation into the biologic importance of these pathways in lymphoma, clinical trials combining different PD-1 inhibitors with other agents are in progress.

Cytotoxic T-Cell Therapy

Chimeric antigen receptor (CAR) T cells

Chimeric antigen receptor (CAR) -T cells are genetically engineered immune effect or cells targeted to tumor cells. Their basic construct includes an extracellular tumor antigen recognition domain, fused to an intracellular T-cell activating signaling domain which most commonly includes the trans membrane adaptor signaling protein CD3ζ [52]. Initial trials of CD19-targeted CAR -T cells focused on CLL with the assumption that this disease as well as indolent lymphomas like FL would allow time for mobilization and engineering of patient T cells without concerns for treatment delays [53-56]. However it was the remarkable efficacy in B-Acute

lymphoblastic leukemia (ALL) that asserted the role of CAR- T cells in the treatment of hematological malignancies. Although preclinical studies were promising no significant clinical responses were observed with first generation CAR until the advent of second generation CAR designs which incorporate intracellular signaling domains such as CD28 and 4-1BB co-stimulatory domains, in addition to the CD3ζ activation domain [54]. Today, third generation CARs with two co-stimulatory domains are available.

Complete remission rates as high as 90% have been reported in relapsed/refractory ALL patients treated with the CD19 CAR -T cell therapy [57,58]. Responses in relapsed/refractory mature B-cell lymphomas have also shown great promise. Kochenderfer et al. [59] reported durable clinical responses of 9-22 months in 12 of 13 evaluable patients (including 8 patients with a CR) with chemo-refractory DLBCL and indolent NHL who received CD19 CAR -T cells. The median age in the study was 56 years (range 30-68 years). Other trials have also reported favorable responses [60,61]. Major adverse events observed in these studies have been fever, hypotension, delirium, and neurologic toxicities, but these have been mostly reversible [62]. Other CAR -T cells being evaluated include CD22 CAR-T (NCT02315612) and CD30 CAR-T for relapsed/refractory HL and ALCL (NCT02274584). A trial of sequential therapy CD19 and CD20 CAR-T for DLBCL (NCT02737085) is also ongoing. Investigators are also evaluating combination of CAR-T cells with other types of immunotherapy.

Bispecific T-cell engagers

Bispecific T-cell engagers (BiTE) are fusion proteins consisting of two antibodies; one component which binds a surface target antigen on cancer cells and the other to CD3 on T cells. Blinatumomab is a CD19/CD3 BiTE that cross-links CD19 on tumor cells with CD3 on patient's cytotoxic T cells. Initial clinical efficacy data were

Table 3: Novel small molecule inhibitors in clinical investigation for relapsed/refractory lymphomas (continued).

Agent	Target	Author	Disease subtypes	Number treated (N)	Response (%)	PFS/DOR (months)	Common toxicities (%)
PI3k/AKT/mTOR Pathway							
Everolimus	mTOR	Witziq [76]	DLBCL, FL, MCL	77	ORR 30	Median DOR (5.7)	Grade 3 or 4 anemia, neutropenia, thrombocytopenia
	mTOR	Johnston PB [79]	HL	19	ORR 47	Median TTP (7.2)	Grade ≥3 anemia, neutropenia, thrombocytopenia pulmonary toxicity
BTK Pathway							
Ibrutinib	BTK	Advani [110]	FL, CLL, MCL, DLBCL	56	ORR 60, CR 16	Median PFS (13.6)	Mostly grade 1 or 2 AEs. Grade 3 or 4 thrombocytopenia, neutropenia and anemia (7-12)
	BTK	Wilson [111]	DLBCL	80	ORR 37 in ABC DLBCL	Median PFS (2)	NR
Bcl-2 inhibitor							
Venetoclax	Bcl-2	Gerecitano [112]	B-NHL	106	ORR 47 (75 in MCL)	Median PFS (17)	Grade 3/4 anemia (16), neutropenia (12), fatigue (6) thrombocytopenia (9)

ABC: Activated B-cell; AE: Aadverse Events; B-NHL: B cell Non Hodgkin Lymphoma; BcL-2: B-cell lymphoma 2; BTK: Bruton Tyrosine Kinase; CLL: Chronic Lymphocytic Leukemia; CR: Complete Response; DOR: Duration of response; DLBCL: Diffuse Large B-cell Lymphoma; FL: Follicular Lymphoma; GCB: Germinal Center B-cell; HL: Hodgkin Lymphoma; MCL: Mantle Cell Lymphoma; mTOR: Mammalian Target of Rapamycin; NHL: Non Hodgkin Lymphoma; ORR: Overall Response Rate; PI3K: Phosphatidylinositol 3-Kinase; PTCL: Peripheral T-Cell Lymphoma; PFS, Progression Free Survival; TTP: Time To Progression

generated in a phase 1 trial of patients with indolent NHL, where partial or complete tumor regression was observed [63]. Topp et al. [64-67] then demonstrated that blinatumomab induced durable minimal residual disease (MRD) negative status in adult patients with ALL who had MRD persistence or relapse after induction and consolidation therapy. Subsequently, the same group conducted a phase 2 trial evaluating clinical efficacy in 36 patients with relapsed/refractory ALL. They reported that single-agent blinatumomab in relapsed /refractory ALL had a CR rate of 69% with median OS of 9.8 months. Given its impressive activity in this group, the drug was recently approved for use in relapsed/refractory Philadelphia chromosome negative B-ALL.

Goebeler et al. [68] recently published their phase I study of blinatumomab in patients with relapsed/refractory NHL, showing an overall response of 69% across NHL subtypes, including ORR 55% in DLBCL. The most common adverse events reported were fever and fatigue which were observed in 86% and 55% of patients respectively. A Phase 1 study of blinatumomab in combination with lenalidomide (NCT02568553) for patients with relapsed NHL is currently underway.

Small Molecule Inhibitors

Immune modulators: Lenalidomide

Lenalidomide is an immunomodulatory agent with antitumor activity particularly in B-cell malignancies. Recent studies have elucidated its mechanism of action via binding to the ubiquitin E3 ligase cereblon, leading to degradation of the transcription factors IKZF1 and IKZF3 [69]. In a phase 2 trial that enrolled 217 patients (median age, 66 years) with relapsed/refractory NHL, lenalidomide demonstrated clinical activity with ORR of 35%. Fifty percent of patients enrolled in that study had DLBCL [70]. In a subsequent study, Hernandez et al. [71,72] observed a differential response to lenalidomide - 52.9% in the ABC subtype versus 8.7% in GCB-DLBCL. Since its activity may be restricted to non-GCB DLBCL and not GCB DLBCL which predominates in AYAs, this agent may not have significant applicability in this population. Activity in HL has

been modest [73]. Combination therapy with other novel agents is being evaluated.

Targeting the PI3K/AKT/mTOR pathway

The mammalian target of rapamycin (mTOR), a downstream effect or of the phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) signaling pathway, mediates cell survival and proliferation. Constitutive activation of the PI3K/AKT pathway and mTOR kinase signaling has been recognized as critical events in lymphomagenesis [74]. In addition, mTOR plays an important role in anticancer drug resistance [75]. A phase 2 trial of single agent mTOR inhibitor everolimus in relapsed/refractory DLBCL resulted in ORR of 30% [76]. Its efficacy and safety in combination with rituximab was also investigated in 26 patients (median age 65 years) with DLBCL who had failed or were ineligible to receive ASCT. The evaluable patients in that study had ORR of 38% [77]. The North Central Cancer Treatment Group (NCCTG) recently reported complete metabolic remission of 96% in 24 patients who received a combination of standard R-CHOP and everolimus as upfront therapy for DLBCL. None of the patients had relapsed after median follow up of 21.5 months. The most common grade 3-4 event was neutropenia (75% of patients) [78]. Everolimus has also showed some activity in HL. Johnston et al. [79] reported ORR of 47% in a cohort of patients with relapsed HL.

Pre-clinical studies combining everolimus and the histone deacetylase (HDAC) inhibitor panobinostat showed synergistic anti-proliferative activity [80]. Phase 1 study combining these two agents in both relapsed/refractory HL and NHL showed that 33% of patients achieved a clinical response including 3 CRs, with ORR 43% and 25% in HL and NHL patients respectively. Disappointingly, none of the DLBCL patients in that study obtained a measurable response [81].

Epigenetic Modulators: HDAC inhibitors

By modifying gene expression, histone deacetylase inhibitors (HDACi see below) have been shown to be active in malignancies including relapsed/refractory lymphomas [82]. Panobinostat demonstrated single agent activity in a cohort of HL patients who had

failed ASCT (ORR 27%) [83]. Notably, a reduction in serum thymus and activation-regulated chemokine (TARC) levels was observed in patients who had disease control suggesting that response could be measured by serial levels of this protein [83,84]. However other HDACi have not shown much clinical benefit in HL [85,86].

Both Belinostat and romidepsin demonstrated durable clinical responses in relapsed/refractory PTCL and are currently FDA approved for this indication [87,88]. Although vorinostat showed modest efficacy in indolent NHL (ORR 28%), [85] it had limited activity in DLBCL (ORR 5.6%) [89]. Pre-clinical studies had suggested the anti-tumor activity of this class of drugs could be potentiated in combination with other agents [90,91], but unfortunately this has been limited by hematologic toxicity, particularly thrombocytopenia [92]. Younes et al. [93] recently reported response rates of 55% in relapsed/refractory DLBCL with CUDC-907 a combined HDAC and PI3K inhibitor. In that study, the combination was quite tolerable with grade 3 or worse thrombocytopenia only reported in 20% of the patients.

Epigenetic Modulators: EZH2 inhibitors

The histone methyltransferase EZH2 is the catalytic subunit of the polycomb repressive complex 2 (PRC2) which is required for epigenetic silencing of chromatin [94]. It is frequently mutated in GCB-DLBCL and FL [95-97], and has become increasingly recognized in different types of cancers as a potential drug target. Building on pre-clinical studies reporting clinical activity in EZH2 mutant NHL [98], there are currently three open phase 1/2 clinical trials evaluating EZH2 inhibitors in relapsed/refractory lymphomas- CPI-1205 (NCT02395601), E7438 (NCT01897571) and GSK2816126 (NCT02082977). Given GCB -DLBCL predominates in AYA lymphoma; this class of drug could have application in this population.

Epigenetic modulators: Bromodomain and Extra-terminal (BET) inhibitors

BRD4 is a member of the BET family of proteins, which also includes BRD2, BRD3 and BRDT. These proteins influence transcription through binding to acetylated histones [99]. BRD4 gained clinical attention after it was described as a partner in the (15;19)-associated fusion oncogene in an aggressive squamous carcinoma called NUT midline carcinoma [100]. While screening for epigenetic regulators in an MLL-induced AML mouse model, Zuber et al. [101] identified this same protein as being critically required for disease maintenance. In the same study, suppression of BRD4 by JQ1, the first in class small-molecule BET inhibitor, led to robust anti-proliferative effects both *in vitro* and *in vivo*. JQ1 also led to down-regulation of MYC transcription and similar activity was seen in xenograft models of Burkitt lymphoma [102]. In addition BET inhibition also down-regulated nuclear factor κB (NF-κB) expression on target genes [103]. Thus, this has generated significant clinical interest as potential therapeutic strategy for c-MYC and NF-κB driven hematological malignancies particularly NHLs. The combination of BET inhibitors and Bruton tyrosine kinase (BTK) inhibitor ibrutinib decreased the growth of ABC DLBCL tumor (relies heavily on NF-κB signaling) in mouse models [104].

OTX015 (MK-8628), a new oral BET inhibitor in early clinical development, showed wide preclinical activity in lymphoma models and demonstrated synergism with several anticancer agents, especially with mTOR and BTK inhibitors [105]. A dose escalation open-label Phase 1 study of this agent which enrolled 45 patients (age range 55-72 years) with hematological malignancies (mostly lymphomas) was recently completed. The most common toxic effects reported were thrombocytopenia (96%) and anemia (91%). With the exception of thrombocytopenia (56%), grade 3-4 adverse events were infrequent [106]. A phase 1 study evaluating CPI-0610, an oral BET inhibitor, in adult patients with progressive lymphoma (NCT01949883) is currently ongoing and recruiting patients.

Targeting BTK pathway

A subset of B-cell malignancies are dependent on signals from the B-cell antigen receptor which is mediated through the BTK pathway [107-109]. Ibrutinib is a small molecule irreversible inhibitor of BTK. In a phase 1 study, ORR of 60% was observed in a cohort that included relapsed or refractory NHL and CLL. Although varied, these responses were observed across the different histology subtypes including DLBCL [110]. Similar to lenalidomide, ibrutinib appeared to have more activity in ABC-DLBCL (ORR 40% versus 5% in the GCB subtype) and thus may have limited utility in AYA NHL patients [111-114]. A study comparing R-CHOP plus ibrutinib versus R-CHOP alone in non-GCB DLBCL is ongoing.

Proteasome inhibitors

Proteasome inhibitors (PI) are able to induce apoptosis in malignant lymphoid cells through inhibition of NF-κB activity [115]. Several other mechanisms have been elucidated including the induction of pro-apoptotic Bcl-2 family proteins as well as caspase-independent non-apoptotic cell death [116,117]. Bortezomib was the first PI to be evaluated in clinical trials. Following its success in multiple myeloma, Fisher et al. [118] showed that this agent had moderate activity in relapsed/refractory mantle cell lymphoma (MCL), with both durable responses and tolerable toxicities. Their observations led to the FDA approval of bortezomib in treatment of relapsed/refractory MCL.

Bortezomib has also been evaluated in other NHLs. Given that NF-κB pathway is constitutively activated in ABC DLBCL, it was rational to suppose bortezomib would provide a clinical benefit in this disease. Combined with R-CHOP, it improved outcomes in previously untreated patients with this disease subtype [119], but only demonstrated minimal clinical activity in heavily pre-treated DLBCL patients [120,121]. Also, a recently published Phase 2 study substituting bortezomib (velcade) for vincristine in front-line-R-CHOP (VR-CAP) showed that VR-CAP did not improve efficacy vs R-CHOP in non-GCB DLBCL [122]. The Cancer and Leukemia Group B (CALGB) conducted a multi-institutional Phase 2 trial of single agent bortezomib in patients with relapsed or refractory classical HL and did not observe any responses [123].

Carfilzomib is a PI, structurally and mechanically distinct from bortezomib. A Phase 1/2 study combining this agent with rituximab, ifosfamide, carboplatin and etoposide (R-ICE) in relapsed/refractory DLBCL (NCT01959698) is currently enrolling patients. PIs have been combined with other novel agents in clinical trials. Tan et al. [109] reported that the combination of bortezomib and the HDACi panobinostat in relapsed/refractory PTCL was safe and had encouraging activity (ORR of 43%). Currently, the phase 1 trial (NCT02142530) is evaluating the combination of carfilzomib and the HDACi Belinostat in relapsed/refractory NHL.

Apoptotic Pathway: BcL-2 inhibitors

B-cell lymphoma 2 (bcl-2) is a key regulator of apoptosis in cancer cells and is over expressed in hematologic malignancies,

including NHL [124]. Venetoclax (ABT-199) is a selective, oral Bcl-2 inhibitor whose impressive activity in CLL [125], led to its approval in CLL patients with 17p deletion. As a single agent, it only showed modest activity in relapsed/refractory DLBCL (ORR 18%) [112], although activity was improved in combination with bendamustine and rituximab (ORR 46%) [126]. Trials evaluating the combination of venetoclax with other agents; obinutuzumab and polatuzumab (NCT02611323), and ibrutinib (NCT02419560) are ongoing.

Conclusion

Multiple promising therapies are emerging which may improve outcomes in patients with relapsed/refractory lymphomas. Understanding the biology of lymphomas in AYAs is critical to the effective application of novel treatment strategies. Future trials in relapsed/refractory lymphomas should be driven by disease biology and efforts should continue to be focused on improving the participation of adolescents and young adults in clinical trials.

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