

The Changing Landscape of Relapsed/Refractory Non-Hodgkin Lymphoma

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Despite significant therapeutic advances in the treatment of patients with aggressive type of non-Hodgkin lymphoma (NHL), up to 40% of patients relapse following standard-of-care chemo-immunotherapy (CIT). Management of relapsed and/or refractory (R/R) DLBCL and other types of aggressive NHL is challenging as no standard of care treatment has been defined in this setting. The overall survival (OS) in refractory disease is rather poor with treatment response and duration often decreasing with each subsequent relapse. Such patients are often referred to a clinical trial program with the hope to improve outcomes with new drugs. Thus, treatment failures are by default the highest priority for the clinical trial investigation. Fortunately, recent decades heralded the development of a spectrum of novel therapeutic modalities for R/R NHL directed against a variety of targets including 1) cell surface (eg, monoclonal antibodies), 2) intracellular pathways (eg, Bruton's tyrosine kinase [BTK], phosphoinositide 3-kinase [PI3K], spleen tyrosine kinase [SYK] and B-cell lymphoma/leukemia 2 [Bcl-2], 3) microenvironment (lenalidomide, PD-1 pathway). In parallel, therapeutic options favoring a specific subtype of DLBCL based on the cell of origin (COO), germinal center B-cell (GCB) vs. activated B-cell (ABC) as identified by gene expression profiling (GEP) platforms, are emerging to facilitate patient selection and optimize responses.

Targeting the Cell Surface: Monoclonal Antibodies

The B-cell surface markers including CD19 and CD20 are expressed at most stages of B-cell development and are present in the majority of B-cell NHL. They play a key role in the B-cell receptor (BCR) pathway, which mediates survival and proliferation by engaging cytoplasmic signaling molecules such as BTK, SYK, PI3K. In addition to rituximab, newer CD20 monoclonal antibodies (mAbs) including obinutuzumab (a humanized glycol-engineered type-2 anti-CD20mAb) and ofatumumab (a first humanized, second-generation anti-CD20mAb) have emerged and have already been approved, in conjunction with chlorambucil, for treatment-naïve chronic lymphocytic leukemia (CLL) [1-3]. Single agent obinutuzumab, given at 1600 mg on day 1, 8 of cycle 1 and 800mg on day 1 of cycles 2-8 in R/R NHL demonstrated an ORR of 55% in indolent (N 40) and 32% in aggressive (N 40) NHL in a phase II (GAUGUIN) trial, which included rituximab refractory patients [4,5]. In a randomized phase II (GAUSS) trial obinutuzumab was significantly more potent than rituximab in follicular lymphoma (FL) patients (N 149) with ORR reaching 44.6% in the obinutuzumab monotherapy vs. 33.3% (p = 0.08) in the rituximab group, respectively [6]. The use of obinutuzumab in combination with chemotherapy is being explored in a phase Ib (GAUDI) study that assigned indolent NHL patients to obinutuzumab with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (N 28) or FC (fludarabine, cyclophosphamide) (N 28). Almost all patients,

including rituximab refractory, showed excellent clinical responses; an impressive overall response rate, ORR 96% (complete response, CR, 39%) was achieved in the O-CHOP arm and ORR 93% (CR, 50%) in the O-FC group, respectively [7]. Further phase III trials are currently ongoing [8].

Anti-CD19 chimeric mAb, blinatumomab, a bi-specific T-cell engaging (BiTE[®]) antibody construct with dual specificity for CD19 and CD3, has also shown promising antitumor activity owing to its ability to bind both CD3+cytotoxic T cells and CD19+B cells simultaneously to enhance cytotoxicity. In a phase II study of continuous blinatumomab infusion significant tumor regression was seen in R/R DLBCL patients (N 21) with ORR reaching 43% (16% CR) [9].

Anti-CD22 IgG4 antibody-drug conjugate (ADC) inotuzumabozogamicin (INO) conjugated to the potent cytotoxic agent calicheamicin has emerged as another exciting therapeutic option. In a phase II trial of INO in combination with rituximab (R-INO) in 63 patients with R/R DLBCL, the ORR was over 28% [10]. A phase I trial evaluating a combination of INO with R-CVP (rituximab, cyclophosphamide, vincristine and prednisone) or R-GDP (rituximab, gemcitabine, dexamethasone, platinum) in NHL is currently ongoing [11].

Anti-CD79b mAb polatuzumab vedotin, an ADC conjugated to the cytotoxic agent monomethyl auristatin E has been studied in a phase I study of R/R NHL and CLL. At the recommended phase 2-dose (1.8 mg/kg), single agent polatuzumab demonstrated ORR of 55% in R/R NHL including DLBCL. Interestingly, no responses were seen in CLL [12].

Anti-CD38 mAb daratumomab, a first-in-class, humanized IgG1κ, was initially approved for the treatment of R/R multiple myeloma [13] and subsequently has entered clinical trials in lymphoma world, including R/R NHL. (NCT02413489) Numerous other mAbs and ADCs are in various stages of development as single agents and in combinations. They are at the forefront of clinical research due to both targeted antitumor activity and favorable tolerability. Rational combinations of mAbs with either chemotherapy or other oncogenic pathway inhibitors will likely lead to enhanced response rates and durable remission.

Targeting the Intracellular Pathways

Over the past decades great research effort was focused on BCR signaling pathway, unraveling its therapeutic importance in B-cell lymph proliferative disorders (LPD). BCR signaling mediates a variety of downstream pathways, including BTK, SYK and PI3K, and plays a key role in both initiation and progression of B-LPDs.

In the past several years ibrutinib, a first-in-class, oral, covalent, irreversible BTK antagonist, has emerged as a breakthrough in targeted therapy for patients with not only CLL but also NHL, specifically mantle

cell lymphoma (MCL). The initial phase II trial of ibrutinib (560 mg PO QD) in MCL (N 111) demonstrated a 67% ORR (21%CR, 47%PR) and median duration of response of 17.5 months [14]. Although response rate in DLBCL was less robust (2/7 patients), ibrutinib appears to have activity in non-GCB DLBCL. Interestingly, in R/R FL patients (N 40) ibrutinib demonstrated a relatively modest ORR of 30% (1 CR and 11 PR) (95%CI: 17-47%); not surprisingly, only 11% of rituximab refractory patients achieved a response as compared to 42% of those with rituximab sensitive disease ($p = 0.06$) [3]. In contrast to monotherapy, ibrutinib combination regimens have greater activity particularly when introduced as front line treatment. In a multicenter phase II study of combination ibrutinib(560 mg PO QD) plus rituximab (375 mg/m² IV once weekly \times 4 weeks) in treatment naive FL (N 60), superior ORR of 82% (CR 30%) was observed at a median follow up of 13.8 months. Median PFS, OS, and Duration of Response were not reached; (12 months PFS 86%, OS 98%) [15]. Similarly a phase I study of combination ibrutinib, rituximab and lenalidomide in untreated FL patients (N 22) was equally encouraging. At the recommended phase II dose (ibrutinib 560 mg, lenalidomide 20 mg) the ORR for all patients was 94% (CR 63%) with median time to response of 5.6 months (range 1.9-18.4), and median time on treatment of 12.6 months (range 3.4-23.4). The 12-month PFS was 86% (95% CI: 54% - 96%) [16]. Taken together, these early data suggest that BTK targeting when combined with other pathway inhibitors is going to emerge as a highly effective treatment strategy in NHL. These therapeutic approaches are being tailored to reflect unique biology, cell or origin and intracellular signaling to match various combinations of targeted agents with the properly selected disease type. A great example of that is the study of ibrutinib in combination with RCHOP in patients with newly diagnosed non-GCB DLBCL (NCT01855750).

PI3K-AKT axis inhibition with idelalisib, a first-in-class, oral, PI3K δ antagonist, has demonstrated promising antitumor activity in R/R indolent NHL (iNHL) [17]. In a phase II trial of idelalisib in iNHL (N=125) the ORR was 57%, including 6% CRs and 50% PRs, with median duration of response reaching 12.5 months and median PFS of 11 months [18]. A dual PI3K δ/γ inhibitor, duvalisib, enhanced the ORR to 65% (25% CR) in a phase I trial of iNHL [19].

Proteins in the BCL-2 family are key regulators of cellular apoptosis. Development of specific inhibitors for anti-apoptotic Bcl-2 proteins is a novel approach to alter the pro-survival and pro-apoptosis balance in tumor cells. Venetoclax is a second-generation BCL-2 inhibitor that is currently studied in a phase-1 dose escalation setting in NHL [20]. A subset analysis of the study focused on R/R DLBCL (N 34) including DLBCL-Richter's transformation (N 7) and primary mediastinal large cell lymphoma (N 2) demonstrating the ORR of 15% (9% CR, 6% PR) with the median duration of response for of only 3.3 months (range: 2-4). Notably, patients with DLBCL-RT, a disease extremely difficult to treat, appeared to have a higher ORR of 43% (all PR); albeit the patient number was small [21]. Among the patients with R/R FL (N 29), the ORR was 34% (10%CR and 24% PR) with the median duration of response of 10 months (range: 1-30) [21]. These results suggest that the optimal role of venetoclax for treatment of DLBCL and FL will be in synergistic combination therapies. Indeed, venetoclax is currently being studied in combination with bendamustine and rituximab (BR) as well as with rituxan or obinutuzumab plus CHOP.(NCT02055820) Interim analysis from a dose-escalation study of venetoclax (50-800 mg) with BR (B 90 mg/m²+R 375 mg/m² \times 6 cycles) in heavily pretreated patients with DLBCL (N16) and follicular lymphoma (N 27) showed a significantly improved ORR 38% (25% CR, 13%PR) in DLBCL, and 78% (30% CR, 48% PR) in FL, respectively. Objective responses were observed across all dose cohorts; since the maximum tolerated dose (MTD) has not been reached, dose escalation (1200 mg) is currently ongoing [22]. When compared to similar dosing of BR alone, previous studies demonstrated

lower response rates in both relapsed DLBCL (N 34) ORR 27% (9% CR, 18% PR) and in FL (N 48) ORR 72% (33% CR, 39% PR) [23].

Thus, the encouraging activity of novel inhibitors of intracellular signaling targets namely the BTK, PI3K and Bcl-2, has provided a strong scientific rationale to conduct further studies particularly utilizing various combinations and permutations of these agents with mAbs, cytotoxic chemotherapy and immunomodulating drugs. Simultaneous targeting of distinct pathways with synergistic inhibitors may enhance efficacy and prolong response duration as well as potentially delay the development of resistance to each monotherapy.

Targeting the Microenvironment

It has been increasingly recognized that lymphoma cells are involved in multiple interactions with the non-malignant cells and stromal elements, the tumor microenvironment. Targeting interactions of tumor cells with their microenvironment opens novel therapeutic opportunities for both CLL and R/R NHL. Lenalidomide, an immune modulatory agent widely used in multiple myeloma and myelodysplastic syndromes, has been investigated in a multitude of NHL preclinical and clinical studies. Its activity in LPDs is thought to occur primarily through immune modulation (eg, T-cell and NK-cell enhancement), anti-proliferative and anti-angiogenic effects. Direct antitumor effects are mediated via its binding to the protein cereblon, altering affinity for E3-ubiquitin ligase substrate of the ubiquitin-proteasome pathway.

Early studies have demonstrated clinical activity of lenalidomide in R/R NHL leading to encouraging combination regimens including lenalidomide (Revlimid[®]) plus rituximab, referred to as "R square". This combination was first tested in relapsed iNHL and, more recently, in MCL(N 38) achieving ORR of 92% (95% CI: 78-98) with high CR of 64% (95% CI: 46-79); 2-year PFS and OS was estimated to be 85% (95% CI: 67-94) and 97% (95% CI: 79-99), respectively [24] Similarly, the combination of Revlimid and RCHOP (R²CHOP) showed excellent activity in R/R DLBCL (N 64) demonstrating an outstanding ORR of 98% (80% CR) with OS reaching 78% (95% CI: 68-90) at 24 months. Notably, in the R-CHOP arm, a 24-month PFS and OS was 28% vs 64% ($P < .001$) and 46% vs 78% ($P < .001$) in non-GCB DLBCL versus GCB DLBCL, respectively. In contrast, the addition of lenalidomide appears to mitigate a negative impact of non-GCB phenotype as no difference in PFS or OS was seen in the R²CHOP arm based on non-GCB and GCB subtype 60% vs 59% ($P = .83$) and 83% vs 75% ($P = .61$) at 2 years, respectively [25]. These data provide further support to testing combinations of biologic adjuncts to standard chemo immunotherapy in a head-to-head comparison with CIT, the results of which have the potential to completely revolutionize our approach to NHL management.

In conclusion, rapid exciting advances are being made in the development of targeted inhibitors with a vast number of novel promising agents to improve outcomes in patients with R/R NHL. The most active therapies are likely to incorporate biologically informed combinations of monoclonal antibodies, intracellular pathway inhibitors and immunomodulators. In addition, immunotherapy with programmed cell death-1 protein (PD-1) and its ligand (PD-L1) antagonists and chimeric antigen receptor-T cells (CART) constitute yet another highly promising modality that although outside of the scope of this discussion, will like revolutionize the treatment of relapsed NHL. Since monotherapy seldom leads to complete remissions, it will be critical to prioritize and strategically combine novel agents with/without cytotoxic therapy to induce deeper and more durable responses. As we are rapidly moving toward a precision medicine approach to the treatment of R/R NHL, we face an unprecedented opportunity to make a remarkable progress and change the course of this disease.

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