Transformative Clinical Trials in Non-Hodgkin and Hodgkin Lymphomas

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Abstract

Dramatic progress in the understanding of underlying disease biology and the development of novel therapeutics has yielded a revolution that is poised to transform the face of lymphoma treatment across a broad spectrum of histologies. Ongoing randomized clinical trials are poised to unseat long-entrenched standards of care in diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma, and Hodgkin lymphoma. Emerging treatment approaches are reviewed, including optimization of existing chemoimmunotherapy platforms, development of chemotherapy-sparing immunotherapy for follicular lymphoma, biologically targeted therapy for subsets of diffuse large B-cell lymphoma, and incorporation of novel agents into the treatment of mantle cell lymphoma and peripheral T-cell lymphoma. Novel therapies in early stage trials with future promise of redefining standards of care are also reviewed for non-Hodgkin and Hodgkin lymphomas, including small molecule pathway inhibitors and advances in immunotherapy.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. S1, S141-6
Keywords: Diffuse Large B-cell Lymphoma, Follicular Lymphoma, Mantle Cell Lymphoma, Novel Agents, Peripheral T-cell Lymphoma

Introduction

Ongoing clinical trials are poised to transform the management of lymphomas more so than at any time since the development of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in 1976 and the approval of rituximab 20 years later in 1997. Phase III randomized trials and early phase trials of novel targeted therapies hold the promise of altering treatment paradigms and improving the lives of patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), and Hodgkin lymphoma. In this article, we will review these clinical trials, which are challenging, or might ultimately challenge, long-held standards of care in lymphoma therapy (Table 1).

Follicular Lymphoma

Initial therapy of FL has long relied on combination chemotherapy, most recently in combination with rituximab, which remains the only drug to have improved overall survival in this disease.[1,2] Numerous rituximab-containing regimens have been compared with one another to help inform the choice of upfront chemoimmunotherapy. A randomized trial that compared R-CHOP (rituximab with CHOP), R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), and R-FM (rituximab, fludarabine, and mitoxantrone) found an inferior progression-free survival (PFS) for R-CVP compared with R-CHOP and R-FM, but with no difference in overall survival.[3] The fludarabine-based therapy proved to be more toxic in that study, and is therefore not an appropriate choice for initial therapy. More recently, a randomized trial that compared R-CHOP with R-bendamustine (rituximab with bendamustine) found an improved complete response rate and PFS favoring R-bendamustine, which also had an improved toxicity profile.[4] As with the previous randomized trial, there was no difference in overall survival. As a result of these studies, appropriate initial chemoimmunotherapy regimens for indolent B-cell lymphomas today includes R-bendamustine, R-CHOP, and R-CVP, with choice of regimen based on weighing the risk and benefit ratio for a given patient.

One challenger to this standard of care is obinutuzumab, a type II anti-CD20 monoclonal antibody with enhanced direct cell killing compared with type I antibodies like rituximab and glycoengineering to enhance affinity for the FcγRIIIa polymorphism and improved antibody-dependent cell-mediated cytotoxicity (ADCC). Obinutuzumab has been proven superior to rituximab in chronic lymphocytic leukemia (CLL), and obinutuzumab-chlorambucil improved complete response rate, achievement of minimal

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Submitted: Dec 19, 2014; Accepted: Feb 3, 2015; Epub: Feb 26, 2015

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.02.006

Table 1 Potentially Transformative Randomized Trials of Initial Treatment for Lymphoma

Patients	Treatment Arms	Primary End Point(s)	ClinicalTrials.gov ID
Follicular Lymphoma, Advanced Stage with High Tumor Burden	R-chemotherapy[a] followed by R maintenance versus O-chemotherapy[a] followed by O maintenance	PFS	NCT01332968
Follicular Lymphoma, Advanced Stage With high Tumor Burden	R-chemotherapy[a] versus R-lenalidomide	CRR and PFS	NCT01650701
DLBCL With Low-Intermediate, Intermediate, or High-Risk IPI Score	O-CHOP versus R-CHOP	PFS	NCT01287741
DLBCL	R-CHOP versus DA-EPOCH-R	EFS	NCT00118209
Non-GCB DLBCL	R-CHOP versus bortezomib-R-CHOP	PFS	NCT00931918
Non-GCB DLBCL	R-CHOP versus bortezomib-R-CHOP	PFS	NCT01324596
Non-GCB DLBCL	R-CHOP versus ibrutinib-R-CHOP	PFS	NCT01855750
DLBCL	R-CHOP versus lenalidomide-R-CHOP	PFS	NCT01856192
Non-GCB DLBCL	R-CHOP versus lenalidomide-R-CHOP	PFS	NCT02285062
DLBCL, Ages 60-80	R-CHOP followed by placebo maintenance versus R-CHOP followed by lenalidomide maintenance	PFS	NCT01122472
Mantle Cell Lymphoma	Induction randomization: BR versus BR-V; Maintenance randomization: R versus R-lenalidomide	PFS	NCT01415752
CD30 + PTCL or ALCL	CHOP versus brentuximab vedotin-CHP	PFS	NCT01777152
PTCL	CHOP versus romidepsin-CHOP	PFS	NCT01796002
Classical Hodgkin Lymphoma, Advanced Stage	ABVD versus brentuximab vedotin-AVD	PFS	NCT01712490

Abbreviations: ABVD = adriamycin, bleomycin, vinblastine, dacarbazine; AVD = adriamycin, vinblastine, dacarbazine; ALCL = anaplastic large cell lymphoma; BR = bendamustine, rituximab; V = bortezomib (Velcade); CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CRR = complete response rate; CHP = cyclophosphamide, doxorubicin, prednisone; CVP = cyclophosphamide, vincristine, prednisone; DA-EPOCH-R = dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; DLBCL = diffuse large B-cell lymphoma; EFS = event free survival; GCB = germinal center B-cell like; IPI = International Prognostic Index; O = obinutuzumab; PFS = progression-free survival; PTCL = peripheral T-cell lymphoma; R = rituximab.
[a]Chemotherapy backbone options are investigator's choice of CVP, CHOP, or bendamustine.

residual disease, and PFS over rituximab-chlorambucil, creating a new standard of care for elderly CLL patients with comorbidities.[5] Despite the superiority of obinutuzumab over rituximab in CLL, however, an improvement in other B-cell lymphomas remains to be established. Notably, rituximab has poorer single-agent activity in CLL relative to other B-cell non-Hodgkin lymphomas, so superiority might be more difficult to show in these histologies. A small single-arm phase II study of obinutuzumab in relapsed indolent B-cell lymphomas found a response rate of 55% with 9% complete responses, and a median PFS of 1 year, which appears similar to the benefit of rituximab alone in relapsed disease.[6] The open-label randomized phase II GAUSS study compared rituximab with obinutuzumab in patients with relapsed indolent B-cell lymphomas not resistant to rituximab and demonstrated a small improvement in overall response rate favoring obinutuzumab (61% vs. 47%; $P = .04$) but no difference in PFS at limited follow-up, tempering enthusiasm for this molecule in FL.[7] An ongoing randomized trial is now seeking to displace rituximab as the standard monoclonal antibody partner in FL by comparing obinutuzumab-based and rituximab-based chemoimmunotherapy as initial treatment (ClinicalTrials.gov NCT01332968). The chemotherapy backbone is at the discretion of the treating investigator—either bendamustine, CHOP, or CVP (cyclophosphamide, vincristine, prednisone), and each arm also includes maintenance monoclonal antibody therapy. A positive result for the obinutuzumab arm would result in a marked shift in the initial treatment of indolent B-cell lymphomas away from rituximab-based treatment.

Despite the entrenched role of chemoimmunotherapy as the initial treatment of choice for high-tumor burden indolent lymphoma patients, rituximab-lenalidomide, often called "R^2," is emerging as a potent chemotherapy-sparing competitor. Lenalidomide has clearly demonstrated activity in FL where it appears to work predominantly by increasing T-cell and natural killer (NK)-cell activation and restoring the immune synapse, thus improving cell-mediated cytotoxicity against malignant cells.[8] The mechanism of action also raises the prospect of synergy when combined with rituximab, which works primarily via ADCC. A randomized phase II study of lenalidomide or lenalidomide-rituximab in relapsed FL indeed demonstrated an overall and complete response rate for lenalidomide alone of 51% and 13%, respectively, compared with an improved 73% and 36% in patients treated with the combination.[9] The median event-free survival was 2 years in the combination arm, approximately twice that observed with lenalidomide monotherapy. Two phase II studies have subsequently evaluated rituximab-lenalidomide as initial treatment of indolent B-cell lymphomas. A single-center study at the M.D. Anderson Cancer Center treated 110 patients, nearly half of whom had FL.[10] Though indications for therapy were not required in this study, 52% of patients met GELF (Groupe d'Etude des Lymphomes Folliculaires) criteria for high tumor burden, 78% of patients had intermediate or high-risk FLIPI (Follicular Lymphoma International Prognostic Index) scores, and approximately a quarter had bulky disease. The overall and complete response rates were 85% and 60%, respectively, in the entire population and a remarkable 98% and 87% in the FL cohort. This complete remission rate compares favorably with traditional chemoimmunotherapy platforms. At 3 years, 78% of patients remain progression-free. A multicenter CALGB (Cancer and Leukemia Group B)/Alliance study of 65 patients with FL also evaluated the combination and found a similar overall and complete response rate of 96% and 71%,