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Prognostic modeling in DLBCL in the era of immunochemotherapy: where do we go from here?

Jean L. Koff¹ and Christopher R. Flowers¹

¹Department of Hematology and Oncology, Winship Cancer Institute, Emory University Atlanta, GA, USA

Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring lymphoid malignancy in the United States, diagnosed in more than 27,000 individuals annually, and accounting for about 25% of adult cases of non-Hodgkin lymphoma.¹ DLBCL represents a significant clinical problem for cancer outcomes research in that it is a curable disease for some, but not all, patients. Although untreated DLBCL patients have an expected survival of less than one year,² with modern immunochemotherapy more than 50% of patients are alive at five years and considered cured.³ More recently, event-free survival at two years has been shown to represent a meaningful endpoint, as patients who achieve that benchmark exhibit similar overall survival (OS) to age- and gender-matched controls in the general population.⁴ Unfortunately, DLBCL patients who experience early relapse or primary treatment failure after standard therapy with R-CHOP experience poor outcomes. In the accompanying article, Howlader and colleagues present a risk-stratified model to estimate DLBCL cure rates in the rituximab era, based on data available in the Surveillance Epidemiology and End Results (SEER) registry.⁵ SEER provides population-based information on cancer incidence and survival in the United States covering approximately 30% of the US population. The model and approach described by Howlader and colleagues can form a foundation for future risk prediction models that incorporate data on known differences in demographic, socioeconomic, clinical, and biological factors. Such models would be useful in supporting individual patients' and clinicians' understanding of the baseline expectation for DLBCL survival as well as patient-specific factors that could alter this course.

Since the 1990s, the combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the standard for DLBCL, following a randomized controlled trial that showed that CHOP was less toxic than intensive regimens and produced equivalent survival. In 2002, a randomized trial comparing CHOP and CHOP plus rituximab (R), the first monoclonal antibody anti-cancer therapy, demonstrated that R-CHOP improved 2-year OS from 57% to 70%.⁶ Follow-up data from this and other randomized trials confirmed the benefits of R-CHOP. For eligible patients with relapsed DLBCL, salvage chemotherapy followed by consolidation with autologous stem cell transplantation has been established as a preferred standard-of-care treatment strategy that can cure at least 30% of relapsed patients as compared to salvage chemotherapy alone, which cures <10%.²

Despite these advances, patients with DLBCL have disparate outcomes based on clinical factors, biologic subtype, race, and even insurance status.^{7–9} Howlader *et al.* have attempted to refine cure estimates by assessing risk-stratified outcomes in a large dataset. This model included: Ann Arbor stage, age at diagnosis, gender, race, Hispanic ethnicity, marital status, a population-level measure of poverty, and crude measure of initial course of therapy assessing chemotherapy or radiation or both. Congruent with prior analyses, worse DLBCL-specific mortality was associated with older age and advanced stage at diagnosis, male gender, black race, Hispanic ethnicity, and not being married.^{8,9} However, several clinical data elements known to impact prognosis are not routinely captured in SEER data. For example, the International Prognostic Index (IPI) score for DLBCL identifies stage 3/4 disease, elevated lactate dehydrogenase (LDH), age >60 years, ECOG performance status 2, and involvement of >1 extranodal site as poor prognostic factors. The laboratory and performance status measures in the IPI are not captured in SEER data for the majority of patients diagnosed during 2002–2011 in the SEER-13 registries that were included in this study. However, IPI data are available for a subset of DLBCL patients in SEER and have been examined in other prognostic models using SEER data.⁸

Moreover, information on the use of R-CHOP or other specific regimens as initial therapy or at relapse are not available in SEER, which limits extrapolation to clinical populations. The authors have carefully selected the study population to include patients treated after 2002, when the use of R-CHOP predominated, but other studies have demonstrated disparities in immunochemotherapy use in the United States even during portions of this time period.¹⁰ More importantly, gene expression profiling (GEP) has identified biologically distinct molecular subgroups of DLBCL – activated B cell-like (ABC) and germinal center B cell-like (GCB) – that differ in molecular pathogenesis and clinical outcome.⁷ Since GEP is not yet available for routine clinical use, immunohistochemistry (IHC) algorithms were developed and validated for the classification of DLBCL into cell-of-origin subtypes. The most commonly utilized algorithm proposed by Hans *et al.* uses CD10, BCL6, and MUM1 to distinguish GCB and non-GCB subtypes, but this method has been shown to misclassify approximately 20% of cases.¹¹ Independent of IPI, GCB and ABC subtypes exhibit significantly different OS in patients treated with R-CHOP using either GEP or IHC classification systems.¹² Additionally, recent advances in understanding mutational landscapes identified concomitant MYC, BCL2 and/or BCL6 chromosomal translocations (in so-called double- or triple-hit lymphomas) as unfavorable prognostic markers for DLBCL.¹³ Genome-wide association studies have even identified single nucleotide polymorphisms that associate with outcomes in DLBCL patients treated with immunochemotherapy, suggesting that host genetics also contribute to prognosis.¹⁴ However, at present there is no unifying, comprehensive model that incorporates all of these parameters. Due to the limitations in the dataset described above, Howlader *et al.* did not account for these known and emerging prognostic factors in this analysis. Modern population-based data sources that include these factors are desperately needed in order to construct comprehensive risk prediction models that include these clinically relevant features.

Until very recently, the genomic features leading to the development of different DLBCL subtypes and variations in clinical outcomes remained unclear. With the advent of high-

throughput sequencing, many high-impact studies have emerged examining mutations and molecular pathways implicated in DLBCL pathogenesis. In an effort to characterize how such a diverse array of mutations impact clinical outcomes, Zhang *et al.* performed whole-exome and transcriptome analysis as well SNP arrays in 1001 DLBCL patients treated uniformly with standard rituximab- and anthracycline-containing regimens for whom complete IPI and survival data were available.¹⁵ In addition to confirming survival associations with cell-of-origin subtype and double-hit status, these authors identified combinations of distinct genetic and expression features that suggest context-dependence for survival associations: For instance, KLHL14 mutations were associated with a very poor prognosis in ABC DLBCL, while mutations in EZH2 and CD70 were associated with a particularly favorable prognosis in GCB DLBCL. As next-generation sequencing becomes more financially feasible, incorporating mutational analyses into routine prognostic modeling holds distinct promise for predicting outcome in this heterogeneous disease. Generating rich data sources like the study of 1001 DLBCLs that capture host and tumor genomics and known clinical prognostic factors from patient samples in population-based or large clinic cohorts will be necessary to produce meaningful prognostic models for DLBCL in the future. Eventually, such datasets may help to establish prediction models that will allow us to limit therapy and therapy-related toxicity for favorable subsets of patients while optimizing directed approaches for poor-risk subsets.

Although the development of such models may seem a daunting task, over the last decade the classification of malignant lymphomas has been continually updated to reflect more specific and advanced analytic techniques for establishing a pathological diagnosis that provides useful prognostic information. The recent revisions in the World Health Organization (WHO) classification system present clearer guidelines that define discrete lymphoma subgroups with distinct diagnostic approaches, clinical expectations, and therapeutic strategies.¹⁶ Notably, ABC and GCB subtypes are delineated under DLBCL, not otherwise specified (NOS), and high-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements now constitutes its own distinct entity. Given the increasing granularity with which DLBCL may be categorized in terms of molecular and cytogenetic analyses, and the association of these factors with certain clinical outcomes, it is conceivable that the next iteration of the WHO classification system may subdivide DLBCL entities even further, à la the current system used for defining multiple acute myeloid leukemia disease entities by specific genetic abnormalities. In anticipation of the increased use of these entities in clinical practice and outcomes research, they should be incorporated into the coding system for cancer registries to facilitate their future use in prognostic and predictive models.

In addition to the development of classification systems to distinguish DLBCL entities with different expected outcomes, numerous treatment strategies exist for addressing poor-risk patients with DLBCL. Dose-adjusted etoposide, cyclophosphamide, doxorubicin with prednisone, vincristine and rituximab (DA-R-EPOCH) represents a more dose-intensive alternative to frontline therapy with R-CHOP that showed a 5-year OS of 84% in a phase II multicenter CALGB study of untreated DLBCL patients. When compared to R-CHOP in the subsequent phase III trial, no difference in efficacy was observed, but subset analyses to determine the effect of cell-of-origin subtypes, age and IPI on outcome between the two

arms are pending.¹⁷ In an attempt to improve response rates to front-line therapy, approaches that incorporate novel agents into an R-CHOP backbone have also been explored, with special attention paid to subtype-specific outcomes. Recent results from a phase III trial looking at obinutuzumab (a novel anti-CD20 monoclonal antibody) plus CHOP failed to show improved efficacy over R-CHOP in previously untreated DLBCL patients.¹⁸ Although initial phase II results suggested that addition of the proteasome inhibitor bortezomib to R-CHOP (VR-CHOP) could ameliorate poor outcomes in non-GCB DLBCL patients, data from a subsequent randomized trial showed no difference in OS between R-CHOP- and VR-CHOP-treated patients with this subtype.¹⁹ Promising phase II findings in non-GCB DLBCL patients treated with the immunomodulator lenalidomide and R-CHOP have prompted randomized studies using this regimen.²⁰ Similarly, investigations involving ibrutinib (a Bruton's tyrosine kinase inhibitor) and R-CHOP, and carfilzomib (a second-generation proteasome inhibitor) and R-CHOP are ongoing. One of the challenges observed in modern randomized controlled trials in DLBCL has been the improved performance of R-CHOP in the control arm^{17–19} compared to observed results in older studies.³ At present, it remains unclear whether these findings arise due to patient selection, changes in modern supportive care or other factors. Prognostic models like the one proposed by Howlader and colleagues can establish modern population-based benchmarks for DLBCL outcomes that can be used for planning future trials.

Extensive work in the fields of epidemiology, genomics, and clinical research provides incontrovertible evidence that the factors dictating DLBCL outcomes are many and complex. Major prognostic features that have emerged in the last 15 years include cell-of-origin subtype and presence of MYC translocation with translocation of either BCL2 or BCL6. As demonstrated by molecular studies in DLBCL, large sample sizes are needed to power important subset analyses sufficiently in this heterogeneous disease, and this concept extends to studies of clinical outcomes as well. Reliable integration of information on cell-of-origin subtype into large databases such as SEER may allow models such as those proposed by Howlader *et al.* to define estimates of cure or relapse with increased precision. One of the most important applications of such models would be to direct either intensification, specialization, or de-escalation of frontline therapy to improve outcomes in high-risk groups while sparing low-risk groups from unnecessary toxicities of therapy. At this time, although great advances have been made in understanding the pathogenic mechanisms underlying the clinical heterogeneity of DLBCL, R-CHOP remains the standard frontline therapy for all patients with DLBCL-NOS outside of a clinical trial. However, multiple novel regimens aiming to capitalize on differences in molecular pathways between ABC and GCB-DLBCL have progressed through early-phase clinical trials, and it seems we are poised to enter a new era of subtype-directed therapy in this disease. As the subclassification of DLBCL becomes increasingly intricate, models that go beyond the clinical parameters of the IPI to include cell-of-origin subtype, genetic abnormalities and patient factors will be important to inform estimates of prognosis and decisions about tailored therapy.

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