More than a lonca-shot: beating the odds in relapsed/refractory diffuse large B-cell lymphoma

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Received: September 11, 2023.
Accepted: September 26, 2023.
Early view: October 5, 2023.

https://doi.org/10.3324/haematol.2023.284056

Recent randomized trials have yielded major advances in management of diffuse large B-cell lymphoma (DLBCL), integrating antibody-drug conjugate (ADC) and CD19-directed chimeric antigen receptor T-cell (CAR T) therapies into modern standards of care. However, relapsed/refractory (R/R) DLBCL becomes successively less curable with each recurrence—and patient comorbidities, residual drug toxicities, logistical requirements, and disease biology become increasingly complex. While single-arm studies have yielded several accelerated drug approvals by the US Food and Drug Administration (FDA), these trials are markedly heterogenous with regard to design, eligibility criteria, duration of follow-up, and logistical requirements.[1-5] In this context, selecting the therapy for R/R DLBCL with the best long-term odds of success—balancing efficacy and risk of toxicity—has emerged a formidable challenge.

Among key therapies approved for 3+ line treatment of DLBCL is loncastuximab tesirine-lpyl (lonca), an anti-CD19 antibody conjugated to a pyrrolobenzodiazepine dimer (PBD) DNA-alkylating cytotoxic payload. Lonca was granted US FDA approval in April 2021, for patients with R/R DLBCL, transformed lymphoma, and high-grade B-cell lymphoma, after two or more prior systemic therapies. This approval was based on findings from the single-arm LOTIS-2 trial, which demonstrated an overall response rate (ORR) of 48% and complete response (CR) rate of 24% with lonca administered intravenously every 3 weeks, for up to 1 year.[1] A number of other PBD-based antibody-drug conjugates have been tested in hematologic malignancies but have met the fate of termination by trial sponsors, or unacceptable myelotoxicity and infection risks.[6] Lonca succeeded in DLBCL where many others failed, as the LOTIS-2 trial exceeded its efficacy primary goal (targeting a 40% ORR) while demonstrating acceptable toxicity, in a highly refractory population (58% refractory to their most recent line of treatment). Nonetheless, follow-up of this study was short and toxicities were significant, including cytopenias, photosensitivity, GGT elevation, and volume overload/pleural effusions; median number of treatment cycles was three, and 6% died of treatment-emergent adverse events. Given the stakes involved in selecting lonca for clinical use, longer-term follow-up and a higher level of detail are warranted from the LOTIS-2 study.

In this issue of *Haematologica*, Caimi *et al.* present longer-term follow-up (now median 7.8 months) of the LOTIS-2 study, reporting a median overall survival of 9.6 months and a median progression-free survival (PFS) of 4.9 months.[7] The study primarily focuses on subsets of patients with CR (n=36 [24.8%]) and those who achieved a long-term CR—that is, were alive in CR without disease progression for ≥1 year (n=16 [11%]) or ≥2 years (n=11 [7.6%]). This long-term report finds many ways to describe and parse the 36-patient CR subgroup, whose median follow-up is 35 months and who received a median of eight cycles of lonca treatment. Neither median PFS nor duration or response were reached, and 2-year relapse-free survival is 72.8%. Baseline characteristics of the CR subgroup, and the long-term CR, are also described in depth. However, given small sample sizes, findings (such as a higher median age, percentage female, and high-grade morphology in long-term CR) are hard to interpret. Notably, no patients with primary refractory disease achieved a CR for 2 years or more, casting doubt on any potential for lonca to cure truly chemorefractory DLBCL. In addition, the high level of detail of the CR subgroup is counterbalanced by lack of new detail on treatment exposure or toxicity with lonca, though reassuringly, neither secondary malignancy (including myelodysplasia) nor late liver toxicity (related to GGT elevations observed on therapy) were observed.

These results underscore the potential for lonca to provide durable responses and extended treatment-free periods, without imparting significant long-term toxicity risk, for a select subset of patients. However, identifying pretreatment

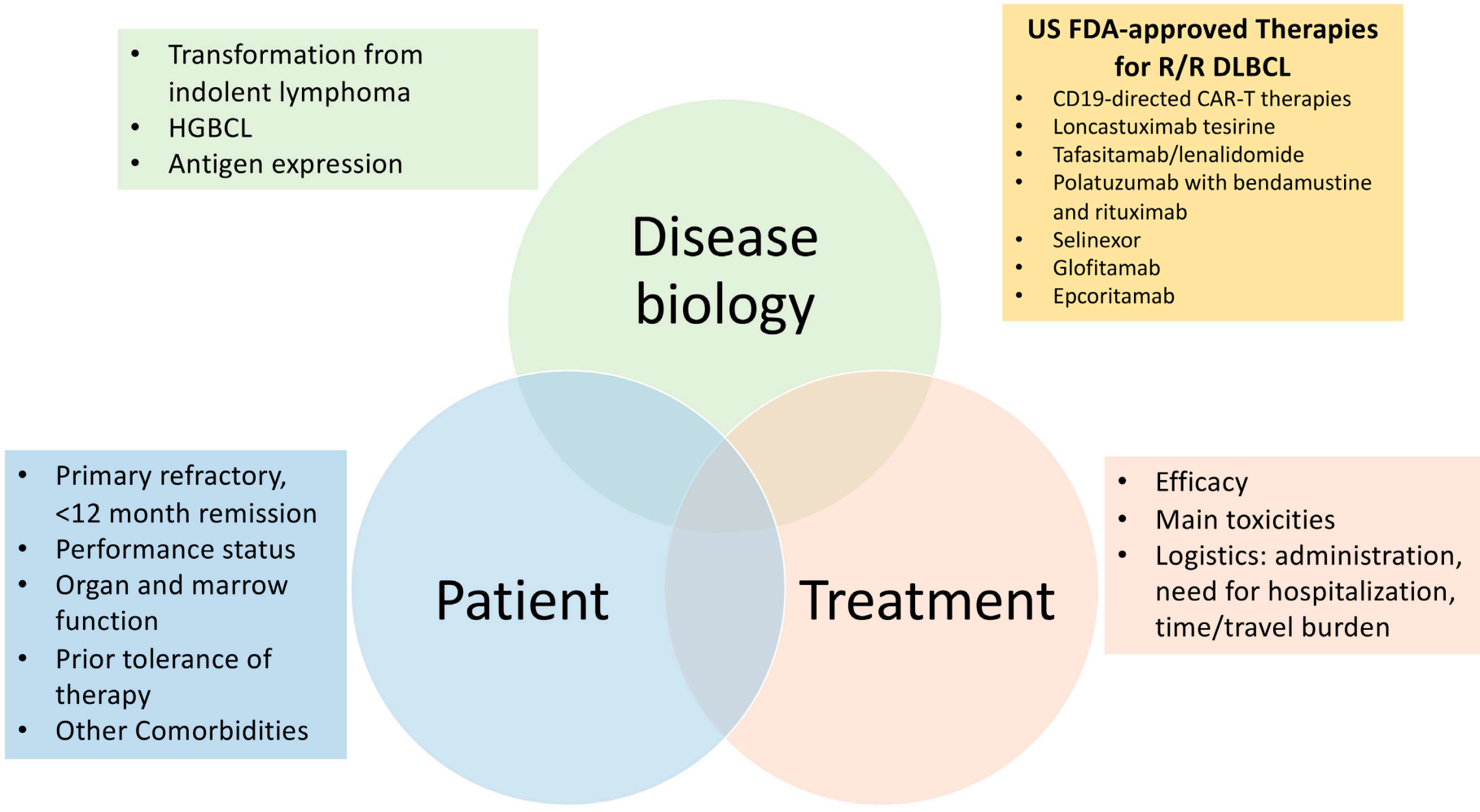

Figure 1. Considerations in selecting among treatments for relapsed/refractory diffuse large B-cell lymphoma in the 3+ line. FDA: Food and Drug Administration; DLBCL: diffuse large B-cell lymphoma. R/R DLBCL: relapsed/refractory diffuse large B cell lymphoma.

patient or tumor characteristics that may predict long-term benefit from lonca remains challenging. Specifically, there are no tissue-based biomarkers for predicting response to lonca. *In vitro* data suggests that CD19 expression, as measured by cell surface protein and RNA level, is associated with the cytotoxic activity of lonca.[8] However, exploratory analyses of CD19 expression by immunohistochemistry on tumor tissue from patients in the LOTIS-2 trial did not reveal any significant correlation with clinical response to lonca.[9] Other DLBCL studies (e.g., brentuximab vedotin in DLBCL) have also failed to note a clear relationship with antigen expression and clinical efficacy, and much work is needed to define biomarkers predicting response to therapy with this agent.[10]

Within the landscape of treatments for R/R DLBCL, and based on LOTIS-2 eligibility, lonca distinguishes itself as a valuable therapeutic option that encompasses high-risk patient populations, including those with high-grade B-cell lymphoma, refractory disease, transformed lymphoma, and those with prior anti-CD19 CAR T-cell therapy. As evidenced in this report, subgroups of these patients with high-risk R/R DLBCL will still achieve durable CR and time off therapy. However, even after reassurance that lonca can help beat long odds, selection of therapy requires nuanced consideration of patient features, toxicities, and logistics (Figure 1). This is particularly relevant in light of two new US FDA approvals of bispecific antibodies with high efficacy (39% CR) but specific toxicity concerns including cytokine-release syndrome and a need for inpatient monitoring.[4,5] The present report by Caimi and colleagues provides a high-resolution look at a small number of durable CR, but no definitive answers. Postmarketing data with lonca, and long-term reports of other agents in the 3+ line setting, are needed to help guide therapeutic choices to beat the odds in R/R DLBCL.

Disclosures

SDS reports consultancy from AstraZeneca, Karyopharm Therapeutics, Kite, Incyte, ADC Therapeutics, BeiGene, AbbVie, Coherus Biosciences (immediate family member), Epizyme, and Numab; research funding from Acerta Pharma/AstraZeneca, Ayala Pharmaceuticals (immediate family member), Bristol-Myers Squibb (immediate family member), Bayer, Denovo Biopharma, Genentech, Ignyta (immediate family member), Incyte, Merck, Portola Pharmaceuticals, BeiGene, ADC Therapeutics, Enterome, Kymera, MorphoSys/Incyte, Nanjing, Portola Pharmaceuticals/Alexion Pharmaceuticals, and Viracta Therapeutics. CH has no conflicts of interest to disclose.

Contributions

CH and SDS wrote the manuscript.

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