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Pola-R-CHP for DLBCL: cost-effective at first glance

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In this issue of *Blood*, Kambhampati et al[1] evaluate the cost-effectiveness of anti-CD79b antibody-drug conjugate polatuzumab vedotin in the upfront treatment of diffuse large B-cell lymphoma (DLBCL). The authors created a model based on data from the POLARIX trial[2] to examine whether pola-R-CHP (polatuzumab vedotin [pola] plus rituximab, cyclophosphamide, doxorubicin, and prednisolone) has improved on progression-free survival (PFS) by sufficient margin compared with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) to make its adoption as frontline therapy for DLBCL cost-effective, at polatuzumab vedotin's current price of $18 720 per cycle.

Despite more than 15 randomized trials comparing novel drug combinations against R-CHOP, R-CHOP has remained the unassailable gold standard for the treatment of newly-diagnosed DLBCL. However, has R-CHOP finally met its match in pola-R-CHP? The phase 3 POLARIX trial, published in late 2021, randomized patients with untreated DLBCL to receive 6 cycles of pola-R-CHP or R-CHOP. POLARIX showed a 6.5% absolute improvement in 2-year PFS (76.7% vs 70.2%, P = .02), with a hazard ratio of 0.73 for progression (95% confidence interval, 0.57-0.95; P = .02), in the absence, thus far, of a difference in overall survival (OS). Since then, regulators, health technology assessment agencies, and clinicians have been grappling with whether pola-R-CHP's modest but significant improvement in PFS warrants its price tag, given the largely comparable toxicity profiles between the 2 regimens.

Kambhampati et al designed a thorough, thoughtful, and timely Markov model to evaluate the cost-effectiveness of pola-R-CHP for newly-diagnosed DLBCL. This involves a hypothetical cohort of patients whose outcomes are modeled based on PFS, OS, and quality of life (QoL) data from POLARIX, the SCHOLAR-1 cohort[3] (a synthetic control arm), and studies of lymphoma QoL outcomes.

An intervention's cost-effectiveness (or otherwise) is predominantly based on its incremental cost-effectiveness ratio (ICER), which quantifies the *relative* benefit of a particular therapeutic strategy compared with the next best strategy, per dollar spent, measured in quality-adjusted life years (QALYs). When assessing whether a strategy is cost-effective, the strategy's ICER is compared with a willingness-to-pay (WTP) threshold, which reflects a country or health care system's evaluation of how much they are prepared to pay for 1 QALY. This approach allows comparisons across different diseases and types of intervention, and the WTP threshold varies substantially between different countries. The UK's National Institute for Health and Care Excellence, for example, uses a WTP threshold of £30 000/QALY (~$38 000 USD), with higher thresholds for treatments for end-of-life care or rare diseases[4]; in the United States, the WTP threshold is typically considered $100 000 to $150 000/QALY,[5] although there is no health technology assessment agency within the US government.

The authors' model finds that pola-R-CHP has an ICER of $84 308/QALY, making it a cost-effective strategy, as its ICER point estimate is below the US-appropriate WTP threshold of $150 000/QALY. When the uncertainty of underlying model inputs was propagated through the analysis, pola-R-CHP was cost-effective in 56.6% of probabilistic sensitivity analysis simulations using a WTP threshold of $150 000/QALY.

Although there is debate among the hematology-oncology community as to the intrinsic value to patients of PFS in the absence of OS,[6] the advantage of a model such as this one is its ability to quantify the financial savings of avoiding subsequent lines of therapy. Of note, the 6.5% between-group difference in PFS corresponded with a 6.5% between-group difference in the proportion of patients in POLARIX who went on to receive a subsequent systemic anti-lymphoma therapy (17% in pola-R-CHP vs 23.5% in R-CHOP) to date.

Although the finding of cost-effectiveness of pola-R-CHP is highly dependent on the maintenance of the between-group PFS difference over longer follow-up, it is likely that this PFS advantage will be maintained. In DLBCL specifically, both because of its aggressive nature and the fact that most relapses occur early in the disease course, PFS is a more reliable surrogate than in most other malignancies.[7,8]

The second key factor that underpins pola's cost-effectiveness is the extremely high price of subsequent therapy, particularly chimeric antigen receptor (CAR) T-cell therapy. CAR T-cell therapy has a list price of $400 000, with total costs of care, including admission, sometimes to intensive care, and adjunct therapies such as tocilizumab, often >$700 000 per patient.[9] Thus, preventing even 1 patient from progression to CAR T-cell therapy can save a substantial amount of money. The authors performed a sensitivity analysis (where 1 or more variables are altered to see the impact on cost-effectiveness) that showed that, if CAR T-cell therapy prices were reduced to match the cost of autologous stem cell transplant, pola-R-CHP would only be cost-effective at a WTP threshold of $150 000/QALY but no longer cost-effective at a WTP threshold of $100 000/QALY.

Bach[10] described this phenomenon as the "New Math of Cost-Effectiveness," whereby 1 drug or strategy is only

cost-effective as the result of the price of an alternate therapy. In this case, pola-R-CHP's cost-effectiveness depends partly on the high price of CAR T-cell therapy. This cuts both ways: as use of CAR T-cell therapy in the second-line setting increases, this will make pola-R-CHP *more* cost-effective; conversely, if somehow CAR T-cell therapy cost or utilization in this clinical context decreased, pola-R-CHP would become less cost-effective. (This "New Math" phenomenon also rests on the assumption that no treatment is not an ethical option, which, in this aggressive malignancy, is indeed the case.)

The third caveat to pola-R-CHP's cost-effectiveness lies in the uncertainty of the model's findings: in only 56.6% of the Monte Carlo simulations was pola-R-CHP cost-effective at a WTP threshold of $150 000/QALY. Fifty-seven percent is close to what one would find if modeling the flip of a coin; a risk-averse decision maker might decide pola-R-CHP is too uncertain to reimburse, depending on both the consequences of a bad decision (ie, the financial and health costs from choosing to fund pola-R-CHP if it is actually cost-ineffective or harmful) and the probability of being wrong (43.4% from this analysis).[11] Cost-effectiveness analysis does not use *P* values, but uncertainty in decision science can relate to the value of future research, in this case highlighting the importance of mature OS data and a more durable PFS benefit.

On first glance, the conclusion from the thorough and independent cost-effectiveness analysis of Kambhampati et al is that pola-R-CHP is cost-effective for newly-diagnosed DLBCL. On deeper inspection, however, pola-R-CHP has only a 56.6% chance of being cost-effective, dependent both on the sustained PFS benefit of pola-R-CHP over R-CHOP with longer follow-up, and on the high price of CAR T-cell therapy.

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SARS-CoV-2 vaccination in CLL: how often is enough?

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In this issue of *Blood*, Shen et al[1] report a significant increase in seroconversion rates after repeated COVID-19 booster vaccinations in patients with chronic lymphocytic leukemia (CLL) and monoclonal B-cell lymphocytosis (MBL). Given that vaccine response in patients with hematologic malignancies, especially in patients with CLL, is often insufficient, further understanding of vaccine immune response is needed for this group of patients at high risk for severe COVID-19. Although the evolution of the pandemic is uncertain, it is likely to remain a serious threat to immunocompromised patients. The data discussed here support the benefits of boosters for these vulnerable patients.

Vaccination has seldom been as decisive as in 2020. Edward Jenner, the father of vaccinology, trusted his project of "sufficient moment to inspire the pleasing hope of it becoming essentially beneficial to mankind" in 1796 but certainly did not anticipate the indispensability of vaccines in the era of a pandemic. Ever since, vaccines have been a key element to prevent infection and to protect the most vulnerable patient groups, such as patients with CLL/MBL. Those patients have a severely impaired immune system due to cellular and humoral defects.[2] Most CLL-directed therapies further aggravate the underlying immunodeficiency, at least transiently, putting patients at an immense risk of a clinical course of severe COVID-19.[3]