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The problem with "unfit": lessons from modern therapy for older patients with Hodgkin lymphoma

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Running heads: Unfit patients with cHL

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The treatment of older adults with classical Hodgkin lymphoma (cHL) remains a major challenge in lymphoma care. Although most younger patients are cured with modern therapy regardless of disease stage, older patients continue to experience inferior survival, greater treatment-related toxicity, and limited representation in prospective clinical trials.(1) The challenge is even greater among patients considered unfit for conventional anthracycline-based chemotherapy, for whom no universally accepted standard of care exists.(2)

In this issue, Lazarovici and colleagues report the results of the phase 2 NIVINIHO study, which evaluated nivolumab followed by response-adapted vinblastine consolidation in treatment-naïve patients with cHL who were considered unfit for standard chemotherapy.(3) Although the treatment was feasible in this vulnerable older population, its efficacy was disappointing. Only 29% of patients achieved a complete metabolic response at the end of treatment, and median progression-free survival (PFS) was less than 10 months—well below expectations for cHL. Yet 2-year overall survival (OS) exceeded 70%, highlighting the complex relationship among disease control, treatment tolerability, and eligibility for subsequent therapy.

Other studies of single-agent immune checkpoint inhibitors (ICIs) in relapsed or untreated cHL have likewise demonstrated limited efficacy compared with chemotherapy-based combinations. In NIVINIHO, only 16% of patients achieved a complete metabolic response after nivolumab alone. This finding reinforces the concept that PD-1 blockade alone is insufficient to provide durable control of newly diagnosed cHL and that even an attenuated cytotoxic component may be important to capitalize on ICI-induced sensitization of Reed–Sternberg cells to chemotherapy.

The most important lesson from NIVINIHO may concern not the activity of nivolumab itself, but rather the difficulty of defining which patients are truly unfit for chemotherapy. The trial enrolled patients using a comorbidity score (the Cumulative Illness Rating Score-Geriatric, or CIRS-G) that was historically used to select treatment intensity for patients with chronic lymphocytic leukemia, with the presumption that eligible participants were unsuitable for anthracycline-containing therapy. Yet, among patients who experienced progression and received subsequent treatment, more than 80% ultimately received chemotherapy, and nearly half received anthracycline-containing regimens. Were these patients genuinely unable to tolerate chemotherapy at diagnosis, or was the fitness assessment insufficiently precise?

The authors acknowledge this possibility. Current instruments such as the G8 and CIRS-G remain imperfect surrogates for physiologic reserve. Older adults with lymphoma constitute an extraordinarily heterogeneous population. Chronologic age, comorbidities, functional status, cognition, nutritional status, and psychosocial support all contribute to treatment tolerance, yet few existing tools adequately integrate these domains into a clinically actionable framework. As a result, patients may be misclassified in either direction.

Despite its limitations, NIVINIHO provides valuable insights into a population that remains poorly represented in clinical research. The discrepancy between poor PFS and relatively favorable OS suggests that many patients who experienced progression were able to achieve meaningful responses to subsequent therapy. Interestingly, we observed a similar discrepancy in a study of single-agent mosunetuzumab for older patients with diffuse large B-cell lymphoma deemed “unfit for chemotherapy” at enrollment, more than 50% of whom received anthracycline-based regimens after progression.(4) These observations suggest that for some unfit older individuals with lymphoma, the initial immunotherapy could serve not as definitive treatment but as a means of stabilizing disease, restoring function, and creating an opportunity to reconsider a more intensive approach later. The challenge moving forward is therefore to develop a more nuanced framework for treatment selection. Rather than classifying patients dichotomously as fit or unfit for chemotherapy, it may be more useful to consider a spectrum of fitness and corresponding treatment options.

At one end of this spectrum are truly frail patients who cannot tolerate clinically meaningful treatment-related toxicity after a multi-dimensional consideration of their geriatric status. For these patients, cure

may not be an appropriate primary therapeutic goal. Single-agent PD-1 blockade or brentuximab vedotin(5) may offer beneficial palliative options. Supportive care alone may also remain appropriate for selected patients who prioritize quality of life over treatment burden near the end of life.

A second group includes patients who are initially unfit but may regain some fitness after initial therapy. These patients may benefit from initial monotherapy with nivolumab—or, alternatively, brentuximab vedotin—because of the favorable balance between efficacy and toxicity and the relatively low risk of rapid disease progression. For patients whose condition improves sufficiently, treatment could subsequently be intensified to nivolumab plus brentuximab vedotin or a chemotherapy-containing regimen.

A third category consists of patients with borderline fitness, for whom conventional chemotherapy remains risky but is not clearly contraindicated. In this setting, nivolumab plus brentuximab vedotin (or nivolumab plus dacarbazine when brentuximab vedotin is contraindicated) offers an attractive balance between efficacy and tolerability, with long-term PFS exceeding 50% in phase 2 clinical trials.(6)

Finally, patients who remain fit despite advanced age should always be considered for curative-intent regimens incorporating chemotherapy. The impressive outcomes achieved with nivolumab-AVD in the randomized S1826 trial, as well as with BrECADD in the older subgroup of the HD21 trial, strongly suggest that age alone should not be viewed as a barrier to modern therapy when physiologic fitness is preserved.(7, 8) For patients unable to receive nivolumab-AVD, sequential—but not concurrent—brentuximab vedotin and AVD is also safe and potentially curative.(9) Combining CIRS-G with functional status based on activities of daily living, as in the simplified geriatric assessment developed by the Fondazione Italiana Linfomi, may provide a useful starting point for distinguishing levels of fitness in both clinical trials and practice.(10) Validating a similar instrument in cHL should be an important research objective.

The central question raised by NIVINIHO is therefore not whether nivolumab should replace chemotherapy in older adults with cHL. Rather, it is whether we can more accurately identify which patients require chemotherapy, which can safely receive it, and which should not. As the therapeutic armamentarium continues to expand, adequate geriatric assessment and fitness evaluation may prove as important as the development of novel agents. Until then, the greatest unmet need in older cHL may not be another treatment, but rather a consistent and validated method for selecting among the tools already available.

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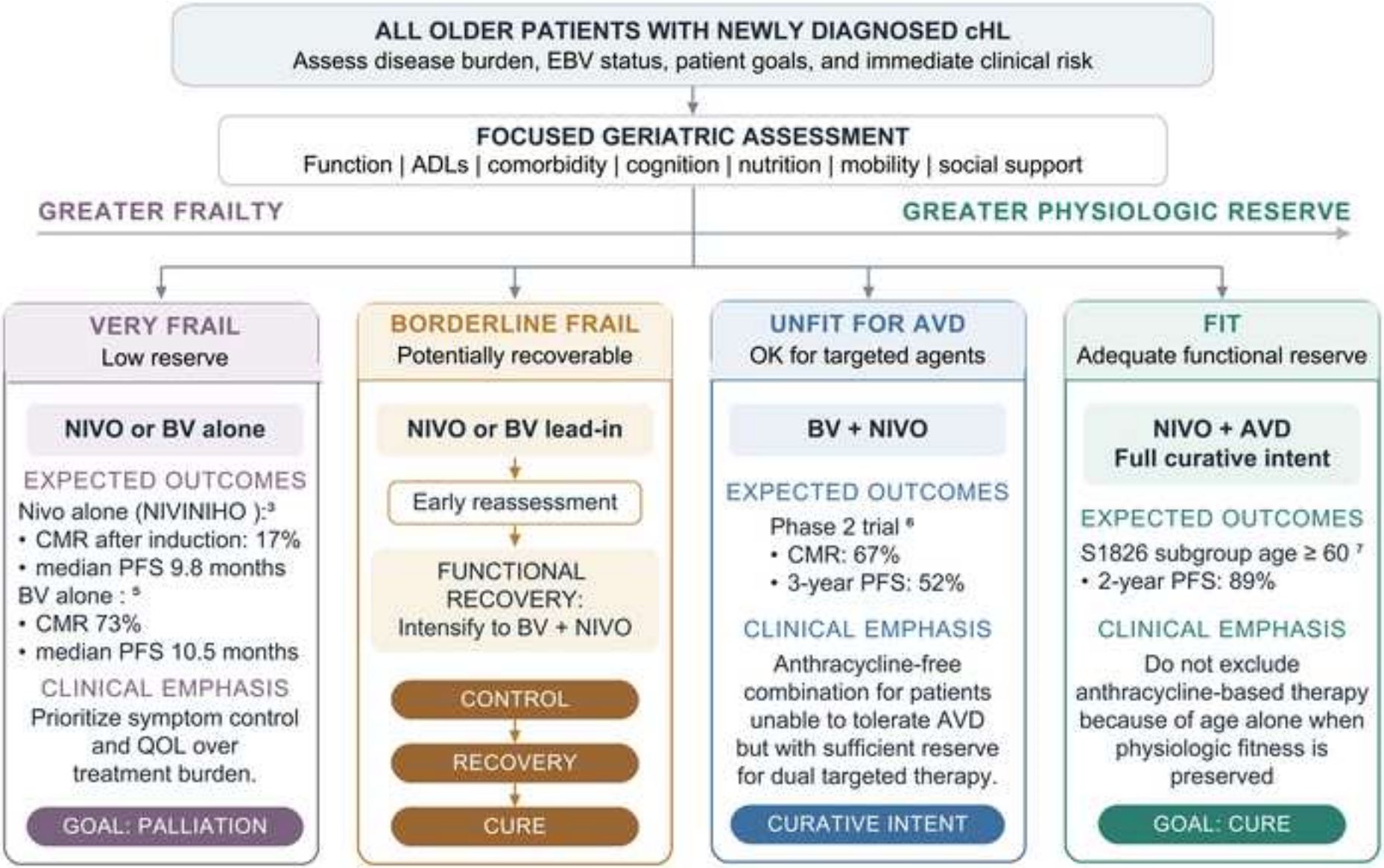
Figure 1. Fitness-adapted treatment framework for older adults with classic Hodgkin lymphoma.

ADL: activities of daily living; AVD: doxorubicin, vinblastine, and dacarbazine; BV: brentuximab vedotin; CMR: complete metabolic response.


ALL OLDER PATIENTS WITH NEWLY DIAGNOSED cHL
Assess disease burden, EBV status, patient goals, and immediate clinical risk
FOCUSED GERIATRIC ASSESSMENT
Function | ADLs | comorbidity | cognition | nutrition | mobility | social support
GREATER FRAILTY
GREATER PHYSIOLOGIC RESERVE
VERY FRAIL
Low reserve
NIVO or BV alone
EXPECTED OUTCOMES
Nivo alone (NIVINIHO):[3]
• CMR after induction: 17%
• median PFS 9.8 months
BV alone : [5]
• CMR 73%
• median PFS 10.5 months
CLINICAL EMPHASIS
Prioritize symptom control and QOL over treatment burden.
GOAL: PALLIATION
BORDERLINE FRAIL
Potentially recoverable
NIVO or BV lead-in
Early reassessment
FUNCTIONAL RECOVERY:
Intensify to BV + NIVO
CONTROL
RECOVERY
CURE
UNFIT FOR AVD
OK for targeted agents
BV + NIVO
EXPECTED OUTCOMES
Phase 2 trial [6]
• CMR: 67%
• 3-year PFS: 52%
CLINICAL EMPHASIS
Anthracycline-free combination for patients unable to tolerate AVD but with sufficient reserve for dual targeted therapy.
CURATIVE INTENT
FIT
Adequate functional reserve
NIVO + AVD
Full curative intent
EXPECTED OUTCOMES
S1826 subgroup age ≥ 60 [7]
• 2-year PFS: 89%
CLINICAL EMPHASIS
Do not exclude anthracycline-based therapy because of age alone when physiologic fitness is preserved
GOAL: CURE