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A ray of hope for early-stage T-cell lymphoma

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Peripheral T-cell lymphomas (PTCL) remain one of the most challenging areas in lymphoma care. Compared with their B-cell counterparts, these diseases are less common, biologically heterogeneous, and historically associated with inferior outcomes (1). Therapeutic progress has also lagged behind that achieved in B-cell lymphomas, where successive generations of targeted therapies, bispecific antibodies, and cellular therapies have transformed the treatment landscape. Consequently, many clinicians continue to approach PTCL with a degree of therapeutic pessimism, viewing poor outcomes as almost inevitable (1).

The rarity of PTCL has further hindered progress, limited the feasibility of large prospective studies and leaving many important clinical questions unanswered. In this context, well-conducted retrospective analyses remain highly valuable. The study by Stuver et al.(2) therefore represents an important contribution to the field and reminds us that PTCL should not be viewed as a single disease entity.

Current treatment recommendations are largely driven by histology and generally apply similar therapeutic strategies across disease stages. In practice, most patients receive six cycles of anthracycline-based chemotherapy regardless of whether their disease is localized or advanced.[3] The present analysis challenges this "one-size-fits-all" approach (3). In this multinational, multicenter retrospective cohort, outcomes of patients with early-stage nodal T-cell lymphomas were evaluated according to treatment strategy. Notably, nearly 90% of patients had either PTCL-NOS or ALK-negative anaplastic large cell lymphoma, making the findings particularly relevant to the most common nodal PTCL subtypes (2).

Patients with stage I disease achieved remarkably favorable outcomes, substantially exceeding what is typically expected for nodal T-cell lymphomas. These findings reinforce the notion that disease stage remains an important clinical and perhaps biological discriminator (2). More importantly, they raise the question of whether treatment intensity should be better adapted to disease extent, a concept increasingly recognized in recent ESMO guidelines (4).

For decades, the dominant paradigm in PTCL has been treatment intensification. Efforts to improve outcomes have focused on adding etoposide to CHOP, consolidating responses with autologous stem cell transplantation, and more recently incorporating novel agents such as brentuximab vedotin. Given the historically poor outcomes associated with advanced-stage disease, this strategy is entirely understandable (3-5).

Yet the present study raises a provocative alternative question: are there subsets of patients for whom less treatment may be sufficient?

The excellent outcomes observed among patients with stage I disease challenge the assumption that all nodal T-cell lymphomas require the same therapeutic intensity. If truly localized disease treated with combined-modality therapy can achieve a five-year overall survival approaching 86%, one must ask whether every patient requires six cycles of systemic chemotherapy or whether selected patients could be cured with a more individualized, stage-adapted approach (2). This concept is not foreign to lymphoma care. Stage-adapted and response-adapted strategies are routinely employed in Hodgkin lymphoma and diffuse large B-cell lymphoma, where the goal is not only to maximize cure but also to minimize unnecessary toxicity (6). By contrast, PTCL has largely remained a “one-size-fits-all” disease. The findings reported here invite us to consider whether treatment de-escalation, rather than further escalation, may represent the next frontier for carefully selected patients with localized disease.

Perhaps the most provocative observation from this study is the apparent benefit associated with combined-modality therapy, particularly in stage I disease. As systemic therapies have improved, the role of radiotherapy has gradually diminished across several lymphoma subtypes. PTCL, however, has not yet experienced the same therapeutic revolution observed in B-cell malignancies. In this setting, the current study provides an important reminder that established treatment modalities should not be prematurely abandoned.

Among patients with stage I disease, combined chemotherapy and radiotherapy were associated with excellent outcomes, with a five-year overall survival approaching 86%. These results suggest that durable disease control may be achievable in a substantial proportion of patients with truly localized disease and support the continued consideration of radiotherapy as part of frontline treatment as reported already previously (7, 8). It raises another question not yet answered: "Are early-stage PTCLs simply diagnosed earlier, or do they represent a biologically distinct subset?

Beyond its therapeutic implications, this study also highlights the importance of early diagnosis. The striking difference in outcomes between stage I and stage II disease reinforces a principle familiar throughout oncology: treatment is most effective when delivered at the right time. This message may be particularly relevant in PTCL, where delays in diagnosis are not uncommon and disease progression can be rapid. Efforts aimed at identifying patients earlier and

accurately defining limited-stage disease may prove just as important as the development of novel therapies.

While prospective validation will be required, these data offer a welcome counterpoint to the longstanding pessimism surrounding nodal T-cell lymphomas. For a subset of patients with truly localized disease, particularly those treated with combined-modality therapy, long-term remission may be more attainable than previously appreciated.

Despite these encouraging results, perhaps the most important unanswered question remains unresolved. The treatment landscape of PTCL is evolving, particularly with the incorporation of brentuximab vedotin into frontline therapy for CD30-positive disease (9). Consequently, the clinically relevant question is no longer whether combined-modality therapy is superior to chemotherapy alone, but whether consolidative radiotherapy remains necessary in the era of brentuximab-containing regimens. For a patient presenting today with stage I ALK-negative ALCL or another CD30-positive PTCL, should the preferred approach be chemotherapy plus radiotherapy, or can modern systemic therapy replace the need for local consolidation? The current study cannot answer this question, as only 11% of patients received brentuximab-based therapy.(2)

Closing this evidence gap should become a priority. The outcomes reported here establish a remarkably high benchmark, with five-year overall survival approaching 86% among patients with stage I disease treated with combined-modality therapy. Future studies must determine whether brentuximab-based approaches can match—or surpass—these results while potentially sparing patients the long-term consequences of radiotherapy.

Ultimately, when the next patient with localized T-cell lymphoma enters our clinic, the goal should not simply be to offer the newest treatment, but to select the strategy most likely to deliver durable remission and survival outcomes at least as favorable as those achieved in this study. The challenge now is not to prove that early-stage T-cell lymphoma can be cured, but to determine how best to achieve outcomes that are at least as good as the 86% five-year overall survival reported here. The next frontier in early-stage T-cell lymphoma may not be escalation, but thoughtful de-escalation.

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Figure 1. Visual summary of key findings in early-stage peripheral T-cell lymphoma, highlighting the prognostic differences between stage I and II disease and the potential benefit of combined modality therapy.

Early-stage T-cell lymphoma

Stage I vs Stage II: A significant prognosis divide

Stage I

66% — 5-year progression-free survival (PFS)

79% — 5-year overall survival (OS)

Stage II

46% — 5-year progression-free survival (PFS)

58% — 5-year overall survival (OS)

The power of combined modality therapy (CMT)

Chemotherapy

Radiation

86%

Survival with chemo + radiation

Stage I patients receiving combined therapy significantly outperformed those receiving chemotherapy alone (74% OS).

The "De-escalation" frontier

Success with CMT suggests selected patients may be cured without high-intensity chemotherapy or transplants.