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Central nervous system management remains an evidence gap in first-line tagraxofusp therapy for blastic plasmacytoid dendritic cell neoplasm. Comment on: "First-line tagraxofusp leads to durable responses and prolonged survival in adults with blastic plasmacytoid dendritic cell neoplasm regardless of fitness level"

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Authors' contributions

SK conceived the Comment and drafted the manuscript. TT critically revised the manuscript for important intellectual content. Both authors approved the final version.

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Pemmaraju et al.[1] recently reported a post hoc analysis of 65 treatment-naive adults with blastic plasmacytoid dendritic cell neoplasm (BPDCN) treated with first-line tagraxofusp (TAG), stratified by the hematopoietic cell transplantation-specific comorbidity index. Objective response rates were 68-80% across risk groups, and some patients from each group proceeded to hematopoietic cell transplantation (HCT). These findings support the feasibility and systemic activity of TAG across a range of comorbidity burdens. However, central nervous system (CNS) staging, prophylaxis, and relapse were not reported. Importantly, analyses confined to patients who ultimately undergo HCT after first-line TAG may underestimate pretransplant CNS relapse, because relapse can delay or preclude transplantation and thereby exclude affected patients from the analyzed cohort. Because CNS involvement may be clinically occult and the CNS penetration and activity of TAG have not been formally established, a systemic response, including complete remission, should not be assumed to indicate CNS control.[2,3] These limitations do not diminish TAG's established systemic efficacy but identify CNS control as a distinct evidence gap.

Imaging may be informative when clinically indicated, but it cannot exclude occult leptomeningeal disease; cerebrospinal fluid (CSF) assessment is therefore central to baseline staging.[3,4] In a prospective series, CSF flow cytometry detected occult disease in six of ten asymptomatic patients evaluated at diagnosis.[4] In a larger retrospective cohort of 103 patients, lumbar puncture was performed in only 29; CNS disease was identified during frontline evaluation in 13 patients and later in ten.[5] However, because testing was incomplete and nonuniform, these data cannot provide an unbiased incidence estimate. Baseline CSF assessment should include both cytology and multiparameter flow cytometry.[4] Flow cytometry improves detection of low-level disease, whereas cytology provides complementary morphologic confirmation.

Evidence for CNS prophylaxis in the TAG era remains limited. Given the clinical relevance of occult disease and the absence of validated risk stratification, CNS prophylaxis should be explicitly considered for patients with negative baseline CSF, although its optimal method and intensity remain undefined.[2,3] Vangala et al. reported a patient who had no baseline lumbar puncture, achieved systemic complete remission after three TAG cycles, and

developed isolated leptomeningeal BPDCN immediately before planned allogeneic HCT. CSF disease cleared after two cycles of high-dose methotrexate plus ifosfamide and four courses of triple-agent intrathecal (IT) therapy.[6] Because no baseline lumbar puncture was performed, this event may represent either initially occult CNS disease or subsequent isolated CNS progression; nevertheless, it illustrates that systemic remission does not establish CNS control. In a Japanese phase I/II study that excluded patients with baseline CNS involvement, CNS involvement was reported at progression in one relapsed/refractory patient among 11 participants.[7]

Comparative evidence is similarly inconclusive. Among responders in a retrospective frontline cohort, CNS relapse occurred in 4% (1/28) after regimens based on hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and in 0% (0/22) after TAG.[8] However, nonstandardized reporting of baseline lumbar puncture, CSF flow cytometry, IT exposure, surveillance, and treatment selection precludes causal comparison or attribution of these outcomes to a specific treatment component.

More recently, a phase II trial combined TAG with hyper-CVAD or mini-hyper-CVD and venetoclax. The protocol specified at least eight IT treatments and incorporated high-dose or mini-dose methotrexate/cytarabine in cycle 5. Among 19 patients, including three with baseline CNS involvement, no CNS relapses were reported.[9] Although clinically encouraging, this small, multimodal study cannot determine whether CNS control resulted from IT therapy, systemic CNS-penetrating chemotherapy, TAG, venetoclax, or their combination.

For patients with negative baseline CSF who receive TAG, planned serial IT prophylaxis is a reasonable practical strategy, particularly when intensive chemotherapy is unsuitable.[2,3] However, no prospective CNS-focused study has established that TAG plus IT is sufficient or defined the optimal IT agents, timing, or number of treatments. Available data also do not establish equivalence between TAG plus IT and an acute lymphoblastic leukemia-type regimen, superiority of either strategy for CNS control, or a routine role for adding systemic high-dose methotrexate or cytarabine to TAG.[6,8,10] Treatment should therefore be

individualized according to age, organ function, disease burden, transplant candidacy, and center experience, with the CNS plan specified separately.

Patients with CSF-positive disease should receive therapeutic, rather than prophylactic, IT dosing until CSF clearance is documented.[2-4,10] When technically feasible, we favor confirming clearance by both cytology and flow cytometry.[4] The role of systemic CNS-penetrating therapy should be individualized.[2,3,10] In patients proceeding to allogeneic HCT, we consider it reasonable to repeat CSF assessment before conditioning; new neurologic or ocular symptoms should prompt immediate reassessment regardless of earlier results. Future TAG trials and BPDCN registries should prospectively report the number and timing of CNS assessments, cytology and flow cytometry results, IT agents and doses, exposure to systemic CNS-penetrating therapy, CNS relapse site and timing, and treatment-related toxicity. CNS outcomes should be analyzed from treatment initiation, not only among patients reaching HCT, to avoid undercounting pretransplant events. Until such data are available, a response to TAG should be viewed as systemic control and not assumed to indicate CNS control; the CNS management plan should be specified and documented separately within first-line therapy.

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