High-dose chemotherapy and autologous stem cell transplantation for secondary central nervous system lymphoma: many are called, but few are chosen

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Relapse of systemic lymphoma within the central nervous system (CNS) is a devastating event with very few long-term survivors after treatment with conventional therapy. High-dose chemotherapy employing CNS-penetrating agents with autologous stem cell support has demonstrated promise in prospective trials in primary CNS lymphoma,[1] and so has naturally garnered attention in secondary CNS lymphomas as well. Single-center retrospective studies have indeed suggested improved outcome favoring this approach, although such analyses have been limited by their retrospective nature, relatively few numbers of patients, and have provided little insight into how many patients with secondary CNS lymphoma are actually candidates for intensive therapy.[2-4]

In this issue of Haematologica, Bromberg and colleagues, on behalf of the International Primary Central Nervous System Lymphomas Study Group, present a larger multicenter retrospective analysis of 92 patients with secondary CNS lymphoma treated in the modern era.[5] Their results confirm the poor overall prognosis in this population with a median overall survival of 7 months. Despite the fact that all patients were treated at stem cell transplant centers, only 29% of patients with CNS relapses underwent high-dose chemotherapy. The primary reasons for not undergoing high-dose chemotherapy were advanced age, comorbid disease, poor performance status, and lack of response to re-induction chemotherapy. Among patients who did undergo autologous stem cell transplantation, however, more than half of them remained alive 2 years later (54%), compared to only 17% of patients treated with less intensive therapy. This certainly suggests a clinical benefit favoring high-dose chemotherapy in these patients, but also reflects the more favorable risk characteristics of patients who are offered transplantation as they tend to be younger with better performance status, fewer comorbidities, and demonstrated chemosensitive disease.

These issues notwithstanding, the findings do validate that a subset of patients with secondary CNS lymphoma may be treated more intensively and enjoy more favorable outcomes, perhaps even cures, than was previously considered possible in the setting of CNS recurrence of systemic lymphoma.

These observations are further supported by data recently published in this Journal from the first prospective study of high-dose chemotherapy in secondary CNS lymphoma.[6] Patients under the age of 65 were enrolled and received sequential induction therapy with high-dose methotrexate, ifosfamide, dexamethasone and intrathecal liposomal cytarabine, followed by high-dose cytarabine, thiotepa, dexamethasone, and liposomal cytarabine. Responding patients then proceeded to high-dose chemotherapy with carmustine, thiotepa and etoposide with autologous stem cell support. Thirty patients were enrolled, 24 of whom ultimately underwent autologous stem cell transplantation. The 2-year time to treatment failure was 49% for the intent-to-treat population, and 58% in patients actually undergoing autologous stem cell transplantation. The overall survival rate for transplanted patients at 2 years was 68%. Although longer follow-up is required, these prospective data demonstrate that high-dose chemotherapy can lead to lengthy remissions in a significant subset of patients who are sufficiently young and healthy to undergo high-dose chemotherapy. They also demonstrate that with intensive CNS-directed re-induction therapy, the majority of patients will achieve a response and be eligible for high-dose chemotherapy consolidation, although advanced age, poor performance status and comorbidities would still represent dominant obstacles to candidacy for intensive therapy in this population.

Based on these retrospective and prospective data and in the absence of randomized trials to guide therapy in this indication, high-dose chemotherapy with CNS-penetrating agents should be considered for all young fit patients with CNS relapse of systemic lymphoma who demonstrate chemosensitive disease to high-dose methotrexate-based re-induction therapy. But what should we do for the majority of patients who present at an older age or with co-morbid disease that obviates the use of intensive therapy? Unfortunately these patients continue to represent an unmet medical need. Radiation to the whole brain or entire craniospinal axis in conjunction with corticosteroids may have palliative benefit, but responses are typically short-lived and are frequently accompanied by significant neurocognitive toxicity.[7] For patients with leptomeningeal relapse, intrathecal therapy with liposomal cytarabine may also offer palliative benefit with reduction in disease burden and associated neurological improvement, though these remissions are similarly not sustained long term.[8] Rituximab, with or without methotrexate, administered via an Ommaya reservoir has been shown to be safe in phase I studies with encouraging evidence of efficacy, and may emerge as an appealing palliative treatment option for leptomeningeal recurrence of non-Hodgkin's lymphoma, but additional data validating this approach are needed.[9,10] This would not benefit the majority of CNS relapses in the modern era, however, which involve the brain parenchyma. Ideally, novel targeted therapies can be studied that target secondary CNS lymphoma with acceptable toxicity profiles. Lenalidomide is an oral immunomodulating agent with clinical activity in relapsed diffuse large B-cell lymphoma, particularly those with a post-germinal center immunophenotype, and warrants evaluation in secondary CNS lymphoma.[11,12] Post-germinal center diffuse large

B-cell lymphoma may also respond to the Bruton's Tyrosine Kinase inhibitor ibrutinib, raising the possibility that this small molecule may ultimately have a role in secondary CNS lymphoma, but this has not been explored to date.[13]

Ultimately, the optimal management of secondary CNS lymphoma is prevention of CNS dissemination in the first place. Incorporation of rituximab with anthracycline-based chemotherapy for initial treatment of diffuse large B-cell lymphoma has reduced the risk of systemic relapse and improved overall survival. Whether systemic rituximab, which has very limited penetration past the blood brain barrier, has reduced the risk of CNS recurrence in the modern era, however, remains a subject of debate with some studies suggesting a risk reduction, and others showing no impact.[14-17] Options for prophylaxis against CNS relapse include intrathecal chemotherapy, or systemic therapy with agents that cross the blood-brain barrier. CNS relapse complicates only approximately 3-5% of all cases of diffuse large B-cell lymphoma,[14,18] so ideally prophylactic therapy may be targeted specifically to high-risk patients and thus spare the majority of patients toxicity of added agents. The most predictive model for increased risk for CNS recurrence is the presence of multiple extranodal sites of disease in concert with an elevated level of lactase dehydrogenase, which has been associated with a CNS recurrence risk as high as 34% in patients treated with R-CHOP in the modern era.[14] Certain anatomic locations have also independently been shown to be associated with an increased risk of CNS recurrence, including the testes, bone marrow, orbit, and paranasal sinuses, among others. These adverse risk factors are well exemplified in the article by Bromberg *et al.* in this issue, in which common features at initial diagnosis in patients who ultimately relapsed in the CNS included the presence of multiple extranodal sites, or involvement of the bone marrow, paranasal sinus, orbit, testis or breast.[5] Of note, only 20 of the 96 patients had received any prophylactic therapy at diagnosis, and this had been almost exclusively with intrathecal chemotherapy.

Despite the ability to identify patients at increased risk of CNS dissemination, a protective benefit for prophylactic therapy has not been definitively established. Intrathecal therapy has been widely employed, although two large prospective clinical trials that included intrathecal prophylaxis for high-risk patients failed to show any protective benefit.[14,18] The current pattern of CNS relapses which predominate in the brain parenchyma in the modern era highlights why treatment directed exclusively at the leptomeningeal compartment may not prove effective at reducing CNS risk. In addition to failing to penetrate the brain parenchyma, intrathecal therapy is also hampered by uneven distribution within the neuroaxis, often leading to subtherapeutic levels in either the lumbar sac or cranial leptomeninges, depending on the site of administration.[19]

Administration of systemic methotrexate may overcome these liabilities by distributing evenly within the cerebrospinal fluid and penetrating the brain tissue. This strategy is routinely employed in regimens for Burkitt's lymphoma and acute lymphoblastic leukemia which carry much higher rates of CNS dissemination, and for which both systemic and intrathecal therapy are typically employed for risk reduction. We retrospectively evaluated 65 patients with diffuse large B-cell lymphoma and high-risk features for CNS dissemination at diagnosis who uniformly received high-dose methotrexate at a dose of 3500 mg/m^2 followed by leucovorin rescue in concert with their R-CHOP therapy, and found only two CNS recurrences in this high-risk population, suggesting value from systemic prophylaxis.[20] The most compelling evidence to support benefit from CNS prophylaxis, however, comes from a randomized trial in aggressive lymphomas comparing standard CHOP to the dose-intensive ACVBP regimen in the pre-rituximab era.[21] Patients in the CHOP arm received no CNS-directed therapy, while the patients treated with ACVBP received systemic methotrexate at a dose of 3000 mg/m^2, as well as intrathecal methotrexate. Patients treated with ACVBP had a significantly lower rate of CNS recurrence compared to that of patients treated with CHOP (2.7% *versus* 8.3%), supporting a protective benefit for CNS prophylactic therapy.

In conclusion, retrospective and prospective data now support the use of high-dose chemotherapy and autologous stem cell transplantation in patients with systemic CNS lymphoma who are sufficiently young and healthy to undergo intensive therapy. Unfortunately, the majority of patients with CNS relapse of systemic lymphoma will not be candidates for such an aggressive approach, highlighting the need to further define optimal prophylactic strategies to prevent CNS recurrence in the first place, and to develop novel agents to target systemic CNS lymphoma with less toxicity than that of traditional chemotherapy and radiation.

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