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CNS lymphoma

To the Editor: Lachance et al¹ report results in 10 patients treated according to a standardized protocol with standard-dose cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Several issues can be raised regarding this report. First, patients with neuroradiographically and pathologically documented parenchymal primary CNS lymphoma (PCNSL) were evaluated for systemic lymphoma. I am unaware of any studies that demonstrate brain parenchymal metastases resulting from systemic non-Hodgkin's lymphoma (NHL). Rather, the common pattern of CNS metastases of systemic NHL is either epidural spinal cord compression or lymphomatous meningitis (LM).²⁻⁶ Therefore, I would submit that a systemic extent of disease evaluation is both unnecessary and irrelevant. However, by contrast, careful staging of the CNS is quite relevant to treatment planning of PCNSL. CNS staging should include slit-lamp examination for possible uveal or vitreous eye disease, CSF cytology for possible lymphomatous meningitis, and spine imaging (either CT-myelography or contrast-enhanced spine MRI) for possible drop metastases. Evidence of eye disease necessitates orbital radiotherapy. Positive CSF cytology or a neuroradiographic pattern compatible with LM necessitates either craniospinal irradiation or involved-field radiotherapy and intra-CSF chemotherapy. Spinal drop metastases necessitate a treatment similar to that described for lymphomatous meningitis. In the paper by Lachance et al,¹ CNS staging of patients with PCNSL appears not to have been uniformly performed and may partially account for the modest outcomes reported.

Second, I am unaware of any compelling data to recommend craniospinal irradiation in the adjuvant treatment of PCNSL. Radiating the entire neuraxis is associated with moderate patient morbidity, often resulting in myelosuppression and radiation enteritis, and may, in addition, compromise the ability to give chemotherapy due to radiation-induced bone marrow injury. Whole-brain or involved-field radiotherapy combined with adjuvant chemotherapy not only obviates the need for craniospinal irradiation but also, as discussed below, results in superior survival outcomes.^{2,3,5-9}

Third, although CHOP is effective for systemic NHL, it might be expected to be less than effective for PCNSL. Of the four active agents in the CHOP protocol, only cyclophosphamide has demonstrated substantial activity against primary brain tumors—at, however, doses two to three times greater than that employed in CHOP.¹⁰ Vincristine and prednisone likely have activity against systemic lymphomas but probably contribute little to regimens directed against CNS tumors. Considerably greater activity and correspondingly improved patient survival have been reported with drug regimens demonstrating substantial brain parenchymal penetration, such as the high-dose methotrexate/intra-methotrexate/radiotherapy/high-dose ara-C regimen described by DeAngelis et al, the CHAD regimen (cisplatin/high-dose ara-C/dexamethasone) described by McLaughlin et al, the radiotherapy plus hydroxyurea followed by PCV (procarbazine/CCNU/vincristine) regimen described by Chamberlain and Levin, the high-dose methotrexate regimen of Glasset al, and blood-brain-barrier disruption regimens described by Neuwelt et al.⁷⁻¹¹ These regimens, which may be equally efficacious against PCNSL in immunocompetent patients, result in 40- to 48-month median survival, a substantial improvement over the whole-brain plus CHOP regimen reported by Lachance et al.¹

I believe the neuro-oncology literature strongly supports the inclusion of adjuvant chemotherapy to involved-field radiotherapy in the treatment of immunocompetent patients with PCNSL; however, chemotherapy regimens superior to CHOP are available and more rationally utilized against these tumors.

Marc C. Chamberlain, MD

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Reply from the Author: We are in agreement with Dr. Chamberlain. We certainly do not advocate CHOP as the ideal regimen for primary CNS lymphoma. In fact, our results argue against its use, and we closed this study early because of the high recurrence rate. The point of our paper was the unusual pattern of intracerebral recurrence at apparently uninvolved sites after an initial response at the primary sites.

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Cabergoline in Parkinson's disease

To the Editor: Lieberman et al¹ and Lera et al² concluded that cabergoline can provide continuous dopaminergic stimulation in patients with Parkinson's disease (PD) when taken orally once a day. It is possible, however, that the improvement after cabergoline—for example, the decrease in "off" time in both studies—is partly due to a peak effect in the morning hours following intake of cabergoline.

Four PD patients participating in an open study of cabergoline in PD with motor fluctuations took cabergoline (mean dose, 8 ± 1.9 mg) at 8 AM for 1 week and at 2 PM for another week. All other medications remained the same. These patients kept diaries of their motor function for 2 weeks from 8 AM until 11 PM by recording at half-hour intervals whether they were "on" or "off." We used paired *t* tests to compare 28 days on which cabergoline was taken at 8 AM with 28 days when the daily intake was at 2 PM.

It appears that the timing of cabergoline administration influences the course throughout the day of hours "off" (figure). When cabergoline was taken at 8 AM the number of hours "off" between 8 AM and 2 PM was 1.4 ± 1.0 hours, fewer than the 2.3 ± 1.0 hours recorded when cabergoline was taken at 2 PM (*p* = 0.000). Intake at 2 PM resulted in 1.4 ± 0.9 hours "off" between 2 PM and 7 PM, fewer than the 2.0 ± 1.1 hours after intake at 8 AM (*p* = 0.024). The results in the evening hours between 7 PM and 11 PM did not differ significantly according to the time of caber-

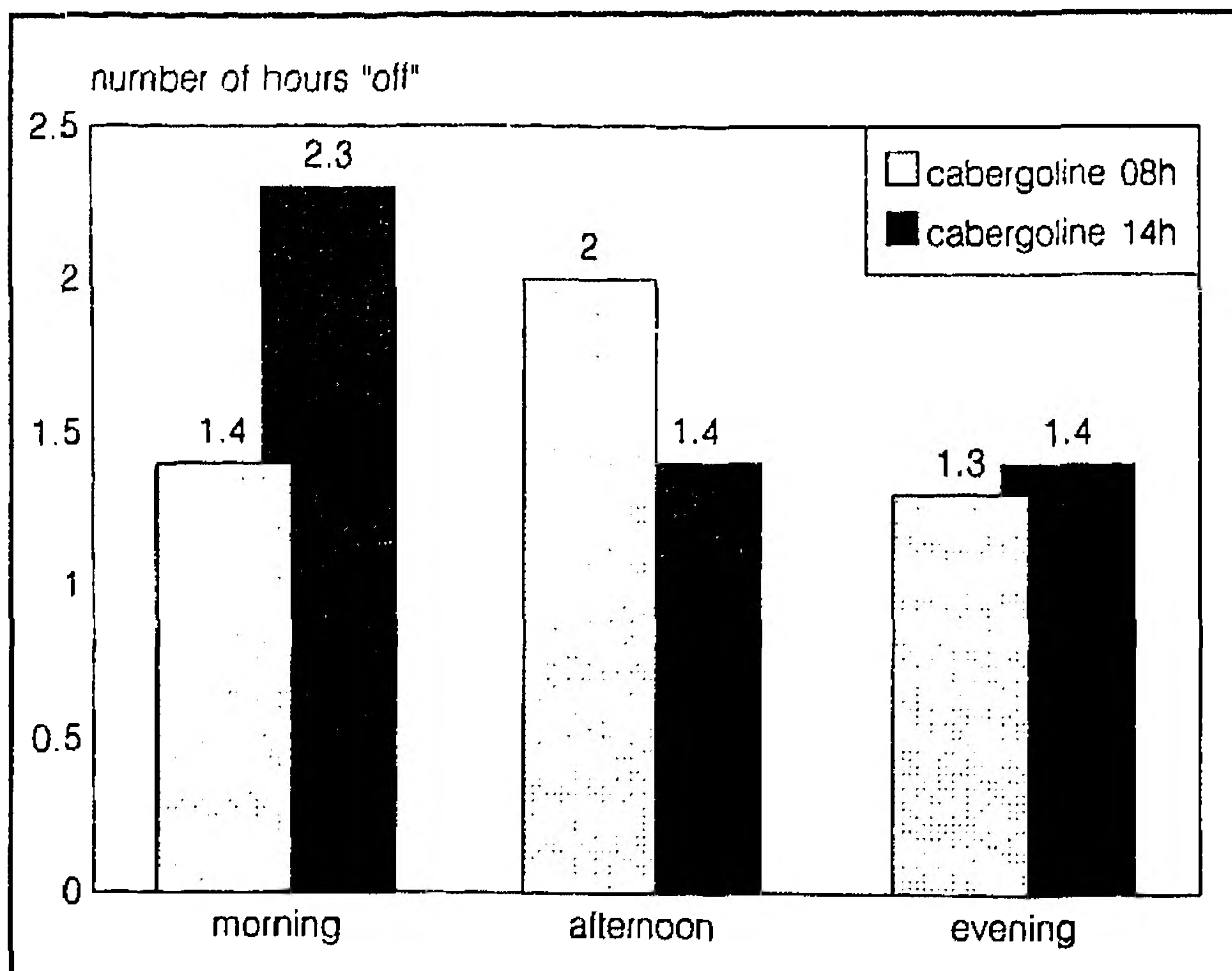


Figure. When cabergoline is administered at 8 AM (08h), there are fewer hours "off" in the morning than when cabergoline is taken at 2 PM (14h). When taken at 2 PM, there are fewer hours "off" in the afternoon than when cabergoline is taken at 8 AM. This suggests that there is a peak-dose effect of cabergoline that does not last throughout the entire day.

goline administration: at 8 AM, "off" = 1.3 ± 0.9 hours; at 2 PM, "off" = 1.4 ± 0.8 hours ($p = 0.74$).

Although the number of subjects is too small to warrant any definite conclusion, our results do suggest a peak-dose effect of cabergoline during the first 5 to 6 hours after administration. This time course matches the course of daily plasma levels of cabergoline (see figure, Lera et al²), showing higher levels 5 to 6 hours after cabergoline intake, especially at the higher dose of 7 mg as taken by our patients.

Lera et al² reported an improvement of early morning akinesia in all patients, and early morning dystonia practically disappeared. This clearly indicates that cabergoline does exert a long-acting dopaminergic effect after the first 5 to 6 hours, but as matters stand at present, further studies will have to be carried out before one can conclude that the easiest way to administer cabergoline (ie, once a day) is also the most effective therapeutic strategy. Despite cabergoline's long-acting properties, administration two or three times a day may prove more beneficial than once daily because the former strategy also implies the beneficial effects of two or three times a peak-dose effect, especially in higher doses of cabergoline.

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Reply from the Author: The study by Horstink et al is interesting although limited in size. Cabergoline may be more effective in some patients when given in two divided doses. In the majority of patients in open studies, the convenience of a once-daily dose outweighs the relatively minor benefit of two divided doses.

Abraham Lieberman, MD
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Reply from the Authors: The observation of Horstink et al is clearly of great practical interest in the attempt to achieve the best possible therapeutic efficacy for cabergoline. A similar situation occurred when pergolide was first experimented with in parkinsonian patients and led to the now-common 3 doses/d application of this dopaminergic agonist. We have observed a sustained motor improvement even after 3 days of stopping cabergoline, and the drug is generally effective in many patients at doses lower than 7 mg/d. We do not believe, therefore, that the observation of Horstink et al is against the idea that cabergoline provides a relatively continuous dopaminergic stimulation. In

fact, there is a major problem with their data in that the observation is apparently based on patients' diaries rather than direct observation by the investigators. Given the relatively small changes in the time "off" (less than 60 minutes) and the well-known lack of reliability of patients' self-assessments, the possibility of a placebo-induced effect should be strongly considered.

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Beethoven's illness

To the Editor: I read Drake's article on Beethoven's possible neurosarcoidosis¹ with much interest and would like to add the following: "Beethoven was an artist, but a man as well." So wrote Franz Grillparzer in his funeral oration for the composer.² Beethoven's music is immortal, but he was endowed with talents and limitations, with strengths and weaknesses of character.² He fell in love often and he had several affairs with "well-born, well-bred women. . . . Although Beethoven frequently regretted not having a wife, he sensed that a stable domestic life would have ill-suited his artistic temperament."²

Nettl³ gave a thorough and complete account of Beethoven and his relation to the medical profession. In addition to constant contact with his friend Professor Franz Wegeler, Beethoven also consulted J.H. Crevelt in Bonn, Johann Nepomuk Hunczovsky (Mozart's doctor), Dr. Ludwig Freiherr von Turkheim in Vienna, Dr. Johann Peter Frank (with whom he consulted about his deafness and diarrhea), and Dr. Gerhardt von Vering, who was Staff Surgeon in Charge to Emperor Joseph II.

Beethoven wrote to Wegeler: "For several days Vering has been applying, to both my arms, vesicants consisting of some bark or other—I expect you know what I mean. This is a most unpleasant form of treatment, because it always robs me of the use of my arms for several days—until the bark has taken proper effect—and is extremely painful to boot. But I must admit that the buzzing and ringing in my ears is now somewhat fainter, particularly in my left ear. Although so far my hearing has not improved in any way . . . my bowels are now on the mend; when I have taken the lukewarm baths for several days, I feel quite well for a week. . . . Sometimes I take a tonic for my stomach. . . . I am now also following your advice and applying herbs to my belly. . . . Vering won't hear of my taking shower-baths." Beethoven also had the habit of drinking enormous quantities of water, and poured a jug of cold water over his head without drying himself! He felt "hot" at work. He also consulted Johann Adam Schmidt, Johann Malfatti, Rohrich, Andreas Wawruch, Andreas Bertolini, Jakob Staudenheim (who sent him for balneotherapy in Karlsbad), and Smettana.

Davies⁴ proposed that the composer suffered from immunopietic complications of his inflammatory bowel disease along with alcoholic cirrhosis of the liver and ototoxicity of the chincona bark (antipyretic). Liston et al⁵ suggested other causes of his deafness: syphilis, otosclerosis, and Paget's disease (remember the thickness of the vault of his skull and his huge forehead!).

Beethoven's deafness had no effect on his musical productivity and creativity,^{5,6} but psychologically he became depressed, unhappy, and isolated. Between bouts of depression, he composed some of his finest material,⁶ and he wrote: "Let your deafness no longer remain a secret—not even in art."⁶

Like other deaf composers—Rossini and Sibelius—Beethoven