decrease in the rate of sustained virologic response (SVR). Little is known about the safety of RBV treatment in patients with concomitant glucose-6-phosphate dehydrogenase (G6PD) deficiency, who are inherently prone to hemolysis.

We prospectively studied changes in hemoglobin (Hb) levels in 112 patients with chronic hepatitis C, associated or not with G6PD deficiency, during and after combination therapy. G6PD activity was tested by a spectrophotometric method. Twenty-six (23.2%) patients (6 women, 20 men) had G6PD deficiency; 4 (3.6%) women had partial G6PD deficiency, who are inherently prone to hemolysis. In a recent Blood article, Schwartz et al reported on the largest cohort of patients with central nervous system (CNS) aspergillosis published to date. In this study, complete and partial responses were recorded in 35% of patients, which is much better than previous reports, when mortality rates were close to 100%. The authors concluded that voriconazole treatment together with

To the editor:

Improved outcome in central nervous system aspergillosis

In a recent Blood article, Schwartz et al reported on the largest cohort of patients with central nervous system (CNS) aspergillosis published to date. In this study, complete and partial responses were recorded in 35% of patients, which is much better than previous reports, when mortality rates were close to 100%. The authors concluded that voriconazole treatment together with

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**References**


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**Figure 1.** Hemoglobin values during and after treatment with pegylated interferon and ribavirin in patients with chronic hepatitis C with and without G6PD deficiency. (A) Mean absolute hemoglobin values (Hb). , patients with G6PD deficiency; , patients without G6PD deficiency. Mann-Whitney tests were performed. *P < .005 and **P < .001 for the comparison between patients with and without G6PD deficiency. (B) Mean changes in hemoglobin levels from baseline. Mann-Whitney tests were performed. †P = .026 and ‡P < .001 for the comparison between patients with and without G6PD deficiency. Data are expressed as means ± SE.
neurosurgical management, whenever feasible, is currently the best approach to treat patients with CNS aspergillosis.1

We fully agree that voriconazole represents an outstanding progress for the treatment of invasive aspergillosis, and probably even more among patients with CNS involvement because of voriconazole pharmacokinetic properties.3,4 Likewise, progress in neurosurgical procedures may allow more effective management of CNS aspergillosis complications in selected cases.2 However, our ability to more easily reduce or reverse the underlying immunosuppression in these patients is another factor that may have played a significant role in the improved outcome of CNS aspergillosis during recent years. Long-term survivors in Schwartz et al’s series were mostly patients with low or chronic underlying immunosuppression, and patients with hematopoietic stem cell transplantation had an inferior outcome compared with all other patients.1 Experimental studies as well as case series strongly suggest that underlying immunosuppression is one of the most powerful predictive factors in invasive aspergillosis.2,6 According to the Infectious Diseases Society of America (IDSA) guidelines, the ultimate response of invasive aspergillosis to antifungal therapy is largely related to host factors, such as the resolution of neutropenia and the return of neutrophil function, lessening immunosuppression and the return of graft function from a bone marrow or organ transplant.3 The emerging repertoire of novel immunosuppressive agents allows more specific tailoring on the immune system,6 while the growing use of adjuvant therapies such as growth factors in neutropenic patients can augment antifungal therapy.2

Response:

Improved outcome in CNS aspergillosis, using voriconazole

We appreciate the comments made by Tattevin and Le Tulzo and fully agree that the type and degree of immunosuppression is likely a prognostic factor in patients with invasive aspergillosis. This is also reflected by the varying response and survival rates in patient subgroups with different causes and severities of immunosuppression in our recent analysis of central nervous system (CNS) aspergillosis.1 However, there is no clear evidence that a low burden of immunosuppression is associated with less than 90% to 100% mortality in patients treated with antifungal drugs other than voriconazole for CNS aspergillosis. It is noteworthy that the response rate of patients with hematologic malignancies was comparable with that of patients with chronic immunosuppression or other underlying conditions. However, 7 (54%) of 13 patients with hematologic malignancies eventually died due to causes unrelated to CNS aspergillosis.1

It is well established that various types of immunosuppression (eg, neutropenia, corticosteroid therapy, and graft-versus-host disease after hematopoietic stem cell transplantation) increase the risk for invasive fungal infections.2,3 However, it is less clear that modulation of immunosuppression always impacts positively on the outcome. Clinico-pathologic data clearly indicate that the use of higher corticosteroid doses and OKT3 is associated with a higher mortality rate in nonneutropenic patients with filamentous fungal infections after allogeneic hematopoietic stem cell transplantation.5 Interestingly, the predominant histopathologic finding in these patients was acellular necrosis, suggesting that corticosteroids severely impair leukocyte trafficking. Although regaining neutrophil function is commonly regarded as an important factor for a successful outcome, recovery from neutropenia was not associated with an improved survival in a recent study evaluating 87 patients with invasive aspergillosis.9 Furthermore, fatal pulmonary complications in patients with mold infections have been reported repeatedly upon recovery from neutropenia.7,9 This is supported by experimental data demonstrating that the neutrophil response is a major cause of tissue damage.7 The current dilemma, especially in patients who have had allogeneic hematopoietic stem cell transplantation and invasive aspergillosis, is to reduce the burden of immunosuppression while maintaining a low risk of graft-versus-host disease. Optimal patient management after restoration of the immune function clearly needs further study.

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References


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To the editor:

The management of meningeal lymphoma in patients with HIV in the era of HAART: intrathecal depot cytarabine is effective and safe

Meningeal involvement in patients with AIDS-related non-Hodgkin lymphoma (ARL) is common; it confers a dismal prognosis, and therapy usually involves frequent lumbar punctures. In 137 individuals with ARL in the era of highly active antiretroviral therapy (HAART), 22 had meningeal involvement at presentation. We compared the use of standard alternating intrathecal methotrexate and cytarabine with a sustained-release formulation of intrathecal cytarabine (DepoCyt) that maintains concentrations in the cerebrospinal fluid (CSF). There were no significant changes in overall survival, the rate of fall of CSF protein, and remission rates defined as absence of lymphomatous cells in the CSF and a CSF protein level less than 0.4 mg/L. DepoCyt appears safe and effective in patients with ARL and meningeal disease and reduces the number of intrathecal administrations required.

Despite the progress that has been made in controlling cancer at most sites in the body, the outcome of individuals affected by meningeal infiltration by cancer remains poor. As few patients with this condition survive for more than several months, the management of individuals with meningeal disease remains a great challenge.1-3 The direct intrathecal instillation of anticancer drugs is one approach that has successfully been used by oncologists, particularly in the treatment and prevention of leptomeningeal leukemias and lymphomas, to circumvent the pharmacologic sanctuary resulting from the blood-brain barrier. Only methotrexate and cytarabine (cytosine arabinoside [Ara-C]) are routinely administered intrathecally, and both are specific to the cell cycle’s S phase. Therefore, both agents would appear most effective when cytotoxic concentrations are maintained. Achieving this has necessitated prolonged and frequent course of lumbar punctures, which are both painful and labor intensive.

An encapsulated microvesicular liposome preparation named DepoCyt (Sykex Pharma, London, United Kingdom) drastically changes the pharmacokinetics of the free cytarabine released5 such that the mean elimination t1/2 of the depot formulation of free cytarabine is 130 to 277 hours, versus 3.4 hours for native cytarabine.6-8 In 2 randomized clinical trials by Glantz et al that have recruited a total of 89 patients,9,10 DepoCyt produced a high response rate, comparable with either methotrexate or free cytarabine, and delayed neurologic progression. The DepoCyt regimen also produced a higher clearance rate of lymphoma from the CSF and prolonged time to neurologic progression compared with conventional intrathecal chemotherapy in a randomized controlled trial.11

DepoCyt has not been evaluated in HIV-1-seropositive individuals. Because patients with ARL have frequent meningeal involvement (a situation complicated by frequent poor compliance in this vulnerable patient group12,13), we compared the efficacy of DepoCyt with that of alternating intrathecal methotrexate and cytarabine.

Since 1996, the start of the HAART era, 137 individuals at The Chelsea and Westminster Hospital have been diagnosed with biopsy-confirmed ARL, including 22 (16%) with meningeal involvement at presentation; these comprised 0.4% of all HIV-1-seropositive individuals with whom follow up was conducted during this time. Meningeal involvement was defined as abnormal enhancement on a brain computerized tomography or magnetic resonance scan and/or the presence of lymphoma cells in the CSF.

In addition to their systemic chemotherapy, they received intrathecal chemotherapy. Up until 2004, this comprised alternating intrathecal methotrexate (12.5 mg) and intrathecal cytarabine (50 mg), given twice a week for 4 weeks, then once a week for 4 weeks, then once a fortnight for 8 weeks, and then monthly until systemic chemotherapy was completed, approximately 18 intrathecal procedures in total.14 Since that time, DepoCyt, a slow-release formulation of cytarabine, has been used alone, comprising a 50-mg intrathecal injection alone every 2 weeks for 2 months followed by monthly injections for 6 months, for a total of 10 intrathecal installations. Each DepoCyt injection was accompanied by 4 mg dexamethasone given orally or intravenously twice a day for 5 days.

There were no significant differences in overall survival between individuals who received either intrathecal alternating...
Improved outcome in central nervous system aspergillosis

Pierre Tattevin and Yves Le Tulzo