normalized after temporary cessation of treatment, and further oral As$_2$O$_3$ therapy was not compromised. Mild skin rashes (grade I) developed in 5 patients and subsided with symptomatic treatment. Headache developed in 2 patients on oral As$_2$O$_3$/ATRA, and subsided when the dose of ATRA was split. None of our patients showed ECG abnormalities of the types previously reported.\(^8\)

Our preliminary results in this pilot study showed that oral As$_2$O$_3$ was highly active in relapsed APL, with an efficacy comparable with intravenous As$_2$O$_3$.\(^3\) The side effects, including the frequency and severity of leucocytosis, LFT derangement, and skin rashes, were also comparable with intravenous As$_2$O$_3$.\(^7,3\)

Cardiac arrhythmias were not found, which was similar to a previous study of intravenous As$_2$O$_3$ in Chinese patients, where arrhythmia was seen in only 1 of 58 patients.\(^2\)

It is important to note that only 4 patients received oral As$_2$O$_3$ as a single agent for CR induction, with the rest having received ATRA or idarubicin before CR was reached. With this limitation, our results showed that oral As$_2$O$_3$ had a short-term efficacy and safety profile similar to intravenous As$_2$O$_3$. A recent study also showed that oral tetra-arsenic tetrasulfide was highly efficacious in APL.\(^10\) However, the long-term efficacy and safety of oral As$_2$O$_3$ compared with intravenous As$_2$O$_3$ will require longer follow-up. Finally, although oral or intravenous As$_2$O$_3$ and hematopoietic stem cell transplantation are effective treatment modalities for patients with relapsed APL, their relative merits are undefined, and further randomized trials will be needed to address this issue.

**References**


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**To the editor:**

**No clinical evidence for CD4$^+$ cell depletion caused by rituximab**

In the recent letter  “Red-cell aplasia due to parvovirus B19 infection in a patient treated with alemtuzumab”\(^1\) Herbert et al inaccurately stated that “the severe CD4 lymphopenia induced by alemtuzumab and other monoclonal therapies such as rituximab for lymphoproliferative diseases is a risk factor for opportunistic infections.”\(^1\)(p1654)

Rituximab (Rituxan; IDEC Pharmaceuticals, San Diego, CA/Genentech, South San Francisco, CA) is an FDA-approved therapeutic monoclonal antibody directed against CD20, an antigen expressed uniquely on cells of the B-lymphocyte lineage, but not on T lymphocytes. In contrast, CD4 is expressed on T lymphocytes, macrophages, and microglial cells, but not on B lymphocytes. Although parvovirus B19 infection has been reported in a patient treated with rituximab,\(^2\) we are not aware of any data suggesting that administration of rituximab leads to a depletion of CD4$^+$ T cells. In fact, flow cytometry data from 166 patients treated with rituximab in a clinical trial showed no diminution of absolute numbers of CD3$^+$, CD4$^+$, CD8$^+$, or natural killer cells.\(^3\)

**M. Wayne Saville, Mark C. Bennyunes, and Pratik S. Multani**

**References**


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**Response:**

**Pure red cell aplasia and alemtuzumab**

Drs Saville and Multani point out an incorrect statement in our recent letter.\(^1\) We had included this statement to highlight the similarity of our case of alemtuzumab-induced pure red cell aplasia (PRCA) to the recent reports of rituximab-associated PRCA (which have now climbed to 3 reports).\(^2,3\) We agree that given the currently recognized mechanisms of action of rituximab, it would be unlikely
to directly deplete CD4⁺ T cells, and the mechanism of rituximab-induced immunosuppression is much more likely to be via suppression of humoral immunity, which may take many months to normalize after exposure. In pointing out our error, it does highlight the importance of the interplay between these 2 arms of the immune system, and also the effect of combining therapies that may influence both B- and T-cell immunity. Indeed, there are recent worrying reports of infections occurring after rituximab administration that are more typically associated with T-cell immunosuppression. Most striking are those of JC papovavirus–related progressive multifocal leukoencephalopathy and cytomegalovirus infection in patients who received periautotransplantation rituximab. Moreover, these patients had an unusually prolonged depression of CD4⁺ cell counts. Delayed CD4⁺ cell reconstitution has been reported by others in patients receiving rituximab after autologous transplantation. Although there may be other reasons contributing to alterations in T-cell immunity in these reports, they highlight that one should not currently dismiss rituximab's potential influence, either quantitatively or qualitatively, on T-cell immunity. Unfortunately, many of the described cases of opportunistic infections in patients treated with rituximab do not report T-cell subsets. Indeed, with the increasing use of rituximab, particularly in combination with therapies that are known to alter T-cell immunity, physicians should carefully consider rituximab’s potential immunosuppressive effects. Furthermore, in an attempt to clarify the impact of rituximab on T-cell immunity, further studies quantitating T cells are warranted.

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References


To the editor:

Allogenic bone marrow transplantation: not a treatment yet for familial Mediterranean fever

We recently heard about the case of an 8-year-old Arabic patient who, following the recent article by Milledge et al., was offered a bone marrow transplantation (BMT) by a private institution to cure his familial Mediterranean fever (FMF). This boy has a very good general constitution but is still suffering from recurrent bouts of fever with abdominal pain, although he has been on colchicine 3 × 0.5 mg a day for 2 years. No alternative drug has been tried. This little boy has no evidence of amyloidosis. While, in this patient, 2 Meta94Val mutations were identified in MEFV, the gene responsible for FMF, no MEFV screening was performed in his HLA-identical younger brother, the designated matched family donor.

We would like to stress the fact that BMT is a life-threatening and expensive procedure that has not proved to be a cure for FMF at this point. We recommend that the following issues be addressed in the rare FMF patients resistant to colchicine: (1) Does the patient indeed suffer from FMF? The diagnosis should be confirmed by a well-experienced clinician and/or by genetic testing. (2) Does he/she really take appropriate doses of colchicine? Is there any possibility of defective absorption of colchicine, allergy, or intolerance to colchicine? (3) Have all medical approaches been exhausted? If the patient truly does not respond to a maximal tolerated dose of colchicine (up to 2-2.5 mg a day, dose split up throughout the day), and if compliance is not involved, other treatments should be discussed, such as interferon α, and possibly thalidomide or anticytokines. (4) In any case, colchicine treatment should not be stopped because of the risk of developing amyloidosis.

Even when the patient is refractory to medical treatment and suffers from intractable and debilitating FMF, it is still debatable whether and when BMT should be considered. We agree that this treatment might possibly improve FMF symptoms, since this disease may be regarded as a hematopoietic disorder and BMT has sometimes shown to work in preliminary trials in other inflammatory disorders, such as rheumatoid arthritis. However, given the morbidity and mortality associated with BMT, and given that FMF is a self-limited disease with an overall good prognosis when colchicine is properly adjusted, we maintain that BMT has no role in the current treatment of FMF in the general medical community and should be contemplated only in the setting of a carefully conducted research protocol, if at all. Moreover, the ethical issue of offering this high-risk, unproven procedure to children is particularly troubling, even in the setting of a well-designed study.

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