

References

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To the editor:

Rituximab administration following autologous stem cell transplantation for multiple myeloma is associated with severe IgM deficiency

Clonotypic B cells are frequently isolated from the peripheral blood of patients with multiple myeloma (MM).¹ These clonotypic B cells may be the clonogenic cells of MM. We have hypothesized that rituximab, a chimeric CD20 monoclonal antibody, may be a useful maintenance therapy in MM after autologous hematopoietic stem cell transplantation (HSCT). The rationale was that CD20 antibody would deplete the clonotypic and, possibly, clonogenic B cells, in the setting of major malignant plasma cell eradication, to reduce the risk of disease relapse. Furthermore, CD20 has been shown in recent studies to be expressed on malignant plasma cells in up to 20% of patients with MM.^{2,3} CD20 antibody has previously been used with limited success to treat patients with MM in a phase 2 study.²

Autologous hematopoietic stem cells (HSCs) were mobilized with cyclophosphamide (3 g/m²) and granulocyte colony-stimulating factor (G-CSF; 10 µg/kg per day) from patients with MM. Two to 3 weeks after stem cell collection, high-dose melphalan (200 mg/m²) was administered intravenously followed 24 hours later by the infusion of at least 2 × 10⁶/kg CD34⁺ cryopreserved autologous stem cells. Rituximab infusion (375 mg/m²) was started on day +30. Each patient received one antibody infusion every 3 months for 2 years or until disease progressed. All patients continued on monthly zoledronate (4 mg) and did not receive any other antimyeloma treatment.

A total of 10 patients have been treated. However, only the 7 patients who have had posttransplantation follow-up periods of more than 12 months were evaluated. One of the 3 patients with follow-up periods of less than 12 months has achieved a complete remission (CR; defined by negative serum protein electrophoresis and immunofixation electrophoresis) and the other 2 patients achieved a partial remission. The immunoglobulin recovery and incidence of infections in this group of patients

were compared to 6 patients with MM who have undergone an autologous stem cell transplantation but without the administration of rituximab.

The total normal immunoglobulin M (IgM) level in all 7 patients was severely depressed following rituximab administration (Figure 1A). Unlike patients with non-Hodgkin lymphoma who received rituximab infusions after autologous stem cell transplantation in which IgG recovery was depressed,⁴ the immunosuppression in patients with MM was observed primarily in IgM and only variably in IgG and IgA (data not shown). The IgM immunosuppression was prolonged and consistent, being observed in all 10 treated patients, regardless of the disease status after transplantation. In contrast, the control group showed normalization of the total IgM levels by 3 months after transplantation. Two patients treated with rituximab received pneumococcal vaccines 12 months after transplantation and neither developed any IgG response to the vaccine. The data indicate that rituximab infusion following autologous transplantation for MM severely impaired B-cell immune reconstitution.

The clinical significance of the IgM immunodeficiency was next examined. Six of the evaluated 7 patients developed moderate to severe infection during the first 12 months after initiation of rituximab infusion. The cumulative infection episodes in these 6 patients are shown in Figure 1B. There were a total of 23 episodes of infection: 21 episodes of pneumonia and 2 episodes of septicemia (one pneumococcus and one *Pseudomonas*). A patient died in CR due to pneumonia. In contrast, only one episode of pneumonia was observed in the control group during the same follow-up period. Therefore, the IgM immunodeficiency probably predisposed the patients to infection.

Of the 7 patients who have had more than 12 months of follow-up periods, 4 had disease refractory to standard induction chemotherapy. Of all the 10 patients treated, 6 achieved CR (2 were in CR before treatment, 2 achieved CR 3 months after treatment, and 2 achieved CR 6 months after starting rituximab). All 4 patients with refractory MM (all had a follow-up of more than 12 months) achieved CR, one before and 3 after starting rituximab. One of the refractory patients has since relapsed, one died of pneumonia 12 months after transplantation, and the other 2 have remained in CR 12+ and 18+ months after transplantation. With a follow-up of 29 months after transplantation, the progression-free survival was 56.5% and the overall survival 71.4%.

Rituximab infusion after autologous stem cell transplantation for MM is therefore associated with severe IgM immunodeficiency and an increased risk of infection. Further works are needed to determine the antitumor activities of rituximab in MM

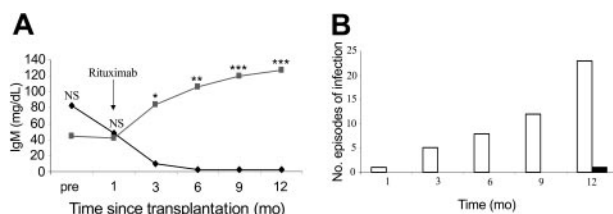


Figure 1. IgM levels and infection risk. (A). Mean total IgM levels before and after starting rituximab infusions (◆), showing significantly lower levels at the 3-, 6-, 9-, and 12-month intervals when compared with those who did not receive rituximab (■) after autologous transplantation. NS indicates not significant; *, $P < .02$; **, $P < .001$; and ***, $P < .0001$. (B) The cumulative episodes of infections in the rituximab group (□) and the control group (■), showing that there was an obvious excess of infective episodes in patients who received rituximab.

in the setting of minimal residual disease, but this should probably only be carried out with special attention to the prevention of infection.

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Rituximab kindly provided free by Genetech, Inc.

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To the editor:

Thrombophilia as a common predisposing factor in pseudotumor cerebri

Pseudotumor cerebri (PTC), also known as idiopathic or benign intracranial hypertension, is related in a significant number of cases to cranial venous outflow obstruction, defined as abnormal venous flow on imaging or venography that may or may not have demonstrable cerebral venous thrombosis which represents an extreme end of the spectrum. Indeed, it has been argued that such a mechanism underlies all cases of PTC, although depending on how assiduously such abnormalities are sought, or on the limitations of imaging modalities, this may not be documented.^{1,2} Recently, we reviewed a large series of PTC patients, including a subgroup in whom the cranial venous outflow was investigated in detail, and found that 31% had evidence of venous outflow obstruction.²

Clearly, there is the possibility of an underlying thrombophilia in PTC patients with cranial venous outflow obstruction with or without demonstrable thrombosis. An association of PTC with systemic lupus erythematosus and an increased incidence of anticardiolipin antibodies have been described; however, the importance of other thrombophilias in PTC with cranial venous outflow obstruction has not been examined.³ Martinelli et al recently described the association of thrombophilia, particularly hyperhomocysteinemia, and overt cerebral vein thrombosis.⁴ The importance of Factor V Leiden (FVL) and the PT20210 mutation had previously been recognized in cerebral venous thrombosis.^{5,6}

We had the opportunity to examine 25 consecutive patients with PTC who were admitted to the neurosurgical unit between 1998 and 2000 and who previously had been assessed for venous outflow obstruction. Only 4 patients had frank cerebral venous thrombosis. The average age was 30 years (range, 11-49 years) and the majority female (23 of 25). All patients had a normal platelet count and screening coagulation studies (activated partial thromboplastin time and prothrombin time). Protein C (PC), protein S (PS; functional), antithrombin levels (AT; STA, chromogenic, Diagnostica Stago, Asnieres-sur-Seine, France), and activated protein C resistance were measured (GradiLeiden V, Gradipore, Australia).

Lupus anticoagulant (LA) was examined using the Dilute Russel Viper Venom Time (DRVVT) and Kaolin Clotting Time (KCT) with confirmation by addition of excess phospholipid. The anticardiolipin antibody (ACA) was measured using an immunoglobulin G enzyme-linked immunosorbent assay and defined as positive if the titer was moderate to high and persisted for more than 6 weeks. Fasting serum homocysteine levels were measured (normal range, < 23 μ M) without oral methionine loading, and all patients confirmed to have normal B12 and folate levels. Mutations for FVL and PT20210 were sought (multiplex amplification refractory mutation system polymerase chain reaction [ARMS PCR]). Fisher exact test was used for statistical analysis.

Thrombophilic defects were detected in 68% (Table 1). There were 2 patients with low PS levels (41% and 43%; normal, 80%-130%), 4 patients with APCR and FVL, 2 with PT20210, 6 with positive ACA, 3 with positive LA (none of whom had positive ACA), and 2 with elevated fasting homocysteine. The rate of FVL and PT20210 is in keeping with rates seen in other thrombotic disorders such as deep vein thrombosis.⁷ We confirm the high frequency of positive LA and ACA as previously described in PTC.³ Again, this is in keeping with other thrombophilic groups.⁸ The possibility exists that ACA positivity is related to an infective cause, and 2 of 6 patients had probable infected shunts at time of testing.

Only one patient had a personal history of deep venous thrombosis (no thrombophilia detected), whereas 3 patients had a family history of venous thromboembolism (all with thrombophilia). There was no history of autoimmune disease and all patients had antinuclear antibody less than a titer of 1:80. No patient was receiving estrogen preparations but, given the striking female predominance, one must speculate on the relationship between endogenous estrogen and underlying thrombophilia. The association between users of oral contraceptives and cerebral venous thrombosis has been described.^{4,6}

A slight predominance of thrombophilic defects was seen in patients with documented venous outflow obstruction: 77% (7 of 9) versus 62% (10 of 16) ($P = .048$). As mentioned, such a diagnosis may be difficult due to the limitations of imaging. It is, therefore, possible that some patients with thrombophilia did, in fact, have undetectable cranial venous outflow obstruction.

In conclusion, there is a high incidence of thrombophilic defects in PTC, particularly in patients with cranial venous outflow obstruction. Cranial venous outflow obstruction may exist in the absence of frank cerebral vein thrombosis and may

Table 1. Thrombophilias in pseudotumor cerebri patients

Thrombophilic defect	Number of patients (%)
All defects	17 (68)
PT20210	2 (8)
FVL/APCR	4 (16)
LA	3 (12)
ACA	6 (24)
PS deficiency	2 (8)
Hyperhomocysteinemia	2 (8)