

Treatment of plasma cell dyscrasias by antibody-mediated immunotherapy.

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The use of serotherapy to treat patients with plasma cell dyscrasias (PCDs) has been sought by us and others. Candidate antigens that have been targeted or proposed for targeting in PCDs include the immunoglobulin idiotype, CD19, CD38, CD54, CD126, HM1.24, and Muc-1 core protein. Unfortunately, many of these antigens are not ideal for use in serotherapy since they are not selectively expressed, are either shed or secreted, or have not been fully characterized. Serotherapy with an anti-CD19 monoclonal antibody (B4) conjugated to a blocked ricin toxin had no significant activity in patients with multiple myeloma (MM). Circulating CD20+ clonotypic B cells have been detected in the circulation of most MM and Waldenstrom's macroglobulinemia (WM) patients. Plasma cells from most WM patients express CD20, but most MM patient plasma cells either lack CD20 or express it weakly. In view of recent successes with anti-CD20-directed serotherapy in other B-cell malignancies, we initiated a phase II trial to study the anti-CD20 monoclonal antibody rituximab (Rituxan; IDEC Pharmaceuticals, San Diego, CA, and Genentech, Inc, San Francisco, CA) in patients with MM. We describe two PCD patients (one with WM and one with MM) who responded to therapy. By flow cytometric analysis, CD20+ plasma cells and B cells present in the bone marrow and peripheral blood of a patient with MM disappeared with response to rituximab therapy. However, residual CD20- tumor cells remained in the bone marrow following rituximab therapy, and after 6 months this patient progressed with CD20- myeloma cells. As a potential strategy to overcome this limitation, we demonstrated that interferon-gamma at pharmacologically achievable levels induced CD20 expression on these CD20- plasma cells, consistent with our recent findings that interferon-gamma is a potent inducer of CD20 expression on MM patient plasma cells and B cells. We also characterize a response to rituximab with a decrease in paraprotein and resolution of anemia in a patient with WM whose response to rituximab is ongoing after 19+ months. This preliminary experience supports the potential use of serotherapy targeting CD20 in PCDs. Our studies further suggest that interferon-gamma may enhance CD20 expression on MM plasma cells, thereby increasing their susceptibility to anti-CD20 monoclonal antibody therapies.