Commentary (Rai/Mehrotra): Current Status of Monoclonal Antibody Therapy for Chronic Lymphocytic Leukemia

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Drs. Nabhan, Dyer, and Rosen provide an excellent and comprehensive review of the therapeutic role of rituximab (Rituxan) and alemtuzumab (Campath) in chronic lymphocytic leukemia (CLL). We take this opportunity to offer our comments concerning these two monoclonal antibodies in CLL.

Pivotal Trials of Rituximab

As the authors mention, in the pivotal study, rituximab was given as a single agent to patients with low-grade lymphoma, once a week for 4 weeks. In that trial, 30 patients with small lymphocytic lymphoma (CLL-equivalent) were included; these patients had only a 13% overall response, whereas 118 patients with follicular lymphomas had a significantly higher overall response rate (60%, \( P < .01 \)).

Nabhan et al cite the report of Winkler et al, in which CLL patients treated with rituximab on a once-weekly schedule for 4 weeks also had a very low (16%) overall response rate. The authors correctly state that "it is believed" that the lower CD20 antigen density and altered pharmacokinetics causing rapid clearance of rituximab in CLL patients may be the reason for the low response rate in this disease. However, when they review the reports of F+R (rituximab used in combination with fludarabine [Fludara])[3,4] in previously untreated CLL patients or FCR (rituximab used with fludarabine and cyclophosphamide [Cytoxan, Neosar]) in both previously treated[5] and previously untreated[6] CLL patients, they observe that the response rates were consistently found to be in the very high range of 70% to 90%.

Nabhan et al cite the Cancer and Leukemia Group B (CALGB) 9712 trial, which revealed that with the F+R concurrent regimen, in which rituximab was given only once a month for 6 months in combination with fludarabine, an overall response rate of 90% was observed, and 33% of these were complete responses. Eventually in the CALGB trial, after additional weekly doses of rituximab for 4 weeks, the complete response rate in the concurrent arm increased to 47%.

Reinterpreting the Rituximab Data

A crucial observation, which most investigators seem to have missed, is that these 90% responses occurred when rituximab was given as infrequently as only once a month, while the results with the more frequent (once-a-week) regimens, as described above, were only in the 13% to 16% range. These observations lead us to question the theory that lower CD20 antigen density and the altered pharmacokinetics of rituximab provide the explanation for poor response with this antibody in CLL. We infer from these data that rituximab is not effective in CLL when it is used as a single agent. On the other hand, this same antibody when used in combination with chemotherapy results in the best response rates ever achieved in previously untreated CLL.

One might argue, however, that the CALGB trial was conducted in previously untreated CLL patients and, therefore, the response rates were very high. In that case, let us cite Nabhan and coauthors’ reference 54, an M. D. Anderson Cancer Center (MDACC) trial in 102 evaluable previously treated (median of two prior regimens) CLL patients-many of them resistant to prior fludarabine. When treated with the FCR regimen (and rituximab, again, on a monthly basis), these patients had a 73% overall response rate, and 23% were complete responses.

With their reference 55, Nabhan et al cite another report from MDACC in which the same FCR regimen was used in 79 previously untreated CLL patients; 95% overall responses were observed, of which 66% were complete responses. Thus, it is clear that in CLL, the degree of expression of CD20...
and plasma antibody levels are not as critical as we have been led to believe, because rituximab has been repeatedly proven to be exceptionally effective in this disease only when it is used in combination with other effective chemotherapeutic drugs. When the response rate reaches 90% to 95%, the variable levels of CD20 expression can hardly be cited as a factor of any significance. Additionally, MDACC data (recently updated at the American Society of Hematology [ASH] congress in December 2002) reveal that 35 (57%) of 61 patients judged to be in complete remission by National Cancer Institute guidelines criteria had molecular-level complete responses (PCR-negative for IgVH gene rearrangement) in previously untreated CLL with the FCR regimen.[7]

We, therefore, wish to highlight the extraordinary efficacy of rituximab in CLL, but note that such efficacy is seen only when the drug is given in combination with other effective chemotherapeutic agents. If these results had been known earlier, we believe that O'Brien et al[8] and Byrd et al[9] would not have embarked upon their investigations with rituximab dosages of, respectively, 2,250 mg/m² every week and 375 mg/m² three times a week.

**Subcutaneous Alemtuzumab**

Nabhan et al have objectively summarized both the efficacy and toxicity profiles of alemtuzumab in CLL and have alerted readers to the potential reactivation of cytomegalovirus (CMV) because of the profound immunosuppressive activity of this antibody. They also mention that the problematic "first dose" reactions seen in many patients during the first 2 weeks of treatment-with intravenous alemtuzumab can be avoided if this antibody is instead given by the subcutaneous route. A recent study by Lundin et al[10] deserves mention in this context. These investigators treated 41 previously untreated CLL patients with alemtuzumab given by subcutaneous injections at 30 mg three times a week. The rigors, rash, nausea, dyspnea, and hypotension observed in most patients given this antibody intravenously were rare or absent in this trial of subcutaneous administration. Transient grade 4 neutropenia was noted in 21% of the patients and infections were rare, but 10% of patients developed CMV reactivation, which was rapidly controlled with ganciclovir (Cytovene) therapy. One patient, allergic to trimethoprim-sulfamethoxazole prophylaxis, developed *Pneumocystis carinii* pneumonia. Injection site reactions of erythema and pain were observed in 90% of patients, but these were transient and, with continued treatment, did not seem to be a problem in most cases. The overall response rate in 38 evaluable patients was 87%; 19% of these were complete responses and 68% were partial responses. Thus, it seems that alemtuzumab by the subcutaneous route should have an important role in the treatment of CLL. A new 30-mg/mL formulation is being developed so that subcutaneous usage will become a practical option.

**Fludarabine/Alemtuzumab Trial**

Nabhan et al mention the ongoing trial of the combination of fludarabine and alemtuzumab. We are now able to provide some preliminary results of this CALGB trial presented recently at the ASH congress in December 2002. In this trial,[11] after four monthly courses of fludarabine in previously untreated 56 CLL patients, intravenous alemtuzumab was given for 6 weeks to 39 patients who had achieved stable disease or a partial or complete response with fludarabine. Among 12 patients who achieved stable disease with fludarabine, 2 improved to a complete response and 7 to a partial response while 3 maintained stable disease following alemtuzumab therapy. Among 24 patients who achieved a partial response with fludarabine, 9 improved to a complete response and 15 had a partial response following alemtuzumab. Overall, 36% of 39 patients receiving both agents achieved a complete response, and 56%, a partial response; thus, the overall response was 92%.

In summary, we believe that these two new monoclonal antibodies have the potential to radically improve the future landscape of CLL therapy when each is used in combination with chemotherapeutic drugs.

**Disclosures:** The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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