Therapy of Advanced B-Lymphoma Xenografts with a Combination of $^{90}$Y-anti-CD22 IgG (Epratuzumab) and Unlabeled Anti-CD20 IgG (Veltuzumab)

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Abstract

Purpose: Antibodies are effective therapeutic agents in cancer, but cures are rarely if ever obtained. Combination therapies are likely to be more effective than a single agent. In this study, the combination of a new unconjugated humanized anti-CD20 IgG, veltuzumab, with a $^{90}$Y-conjugated humanized antibody to CD22 (epratuzumab) was evaluated for the treatment of B-cell lymphoma in a nude mouse model system.

Experimental Design: Nude mice were grafted with the Ramos human B-lymphoma and treatment initiated when tumors were >0.1 cm$^3$. In most experiments, mice were injected first with unconjugated anti-CD20, then with $^{90}$Y-anti-CD22 1 day later. Additional weekly injections of the unconjugated veltuzumab were administered for 3 weeks. Controls included a single agent only and a nonreactive control radiolabeled antibody.

Results: Unconjugated anti-CD20 veltuzumab alone did not have a significant therapeutic effect, even at a total dose of 2.5 mg per mouse. The $^{90}$Y-anti-CD22 epratuzumab alone induced marked regressions of all tumors, but they regrew in a few weeks. The combination of these agents cured ~80% of the mice. A nonreactive control antibody labeled with $^{90}$Y, used without veltuzumab, had no therapeutic effect. The therapeutic effect of $^{90}$Y-epratuzumab required the maximum tolerated dose of radioactivity, which was 160 $\mu$Ci per mouse.

Conclusions: These studies illustrate how combinations of unconjugated and radioconjugated antibodies against different B-cell markers can improve therapeutic outcome, and offer a new therapeutic paradigm for the treatment of B-cell lymphomas.

Treatment of non–Hodgkin’s lymphoma with rituximab constitutes a paradigm shift in therapy. Rituximab therapy results in a ~50% initial response rate (~10% complete response) in patients with previously treated follicular non–Hodgkin’s lymphoma, and although it is not curative, disease progression can be forestalled with re-treatment or maintenance therapy (1–3). As with other antibodies (Ab) in current clinical use, rituximab is most effective when combined with other therapeutic modalities, such as chemotherapy (4), and may also be complemented by other biologicals, such as the anti-CD22 Ab, epratuzumab (5), and the anti-CD80 Ab, galiximab (6). CD20-based radioimmunotherapy, with $^{90}$Y or $^{131}$I conjugates, has shown better objective response rates than naked anti-CD20 Abs (3, 7), yet has not achieved as extensive a role in non–Hodgkin’s lymphoma management as rituximab. A potential limitation of current protocols for the use of radiolabeled anti-CD20 IgG is that a large dose of unlabeled anti-CD20 Ab is injected before the radioconjugate, called predosing. This was found to be necessary to improve uptake of the radiolabeled Ab in the tumor (8), presumably because it blocks the large amount of antigen present on normal B cells in patients. However, despite careful selection of the dose of the unconjugated Ab used, it is evident that predosing may also inhibit uptake into the tumor of the subsequently injected radiolabeled Ab. For example, in a mouse model, Gopal et al. (9) showed that a predose of rituximab inhibited the binding of and therapy with radiolabeled rituximab, but not with a radiolabeled anti-CD45 Ab. Clinical studies have shown encouraging antitumor responses with a $^{90}$Y-labeled anti-CD22 Ab, epratuzumab (10, 11), which has a more restricted specificity for B cells than an anti-CD45 Ab. Therefore, we evaluated the combination of an anti-CD20 Ab, veltuzumab, with a radiolabeled anti-CD22 Ab, epratuzumab. In vitro studies suggested that tumor CD22 expression can be up-regulated by prior treatment with rituximab (5), which might enhance uptake of the radiolabeled epratuzumab.

Other factors make this combination promising. The high-energy $\beta$-particle emitted by $^{90}$Y has a long tissue path length, enabling cell killing even if the Ab does not fully penetrate the tumor, and even if there are antigen-negative subpopulations. However, also because of the long path length of the radiation emitted, single cells or micrometastases are not good targets for...


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90Y-Ab therapy (12). In contrast, single cells are suitable targets for unconjugated Abs because they are readily accessible. Thus, the two forms of treatment can act cooperatively in reducing larger disease burdens, as well as scavenging smaller pockets of disease.

The mechanism of action of unconjugated anti-CD20 Abs, including veltuzumab, has been extensively investigated, but is not fully resolved (2, 4, 13), probably partly because the different animal models used by various investigators may depend on different mechanisms. In humans, an important role for Ab-dependent cellular cytotoxicity has been established, there is evidence that complement activation may be important (13, 14), and in vitro data suggest that apoptosis induction may play a role. In any case, for our present purpose, it is sufficient to note that the mechanism of action of the veltuzumab is certainly different from that of the $^{90}$Y-epratuzumab. Even unconjugated, these two Abs seem to have different mechanisms of action (15).

The unconjugated Ab used was the humanized veltuzumab, which has the epratuzumab backbone and similar hyper-variable regions to rituximab (5). As the radiolabeled Ab, we selected an anti-CD22 humanized Ab, epratuzumab, because this has been found to be an effective investigational therapeutic in patients (10). The model used was Ramos lymphoma cells growing s.c. in nude mice, and the mice were treated when the tumors were established. Because these tumors grow very rapidly, this is a challenging model for therapy. The data presented show that this type of combination therapy seems to be advantageous, and potentially curative, in this animal model.

Materials and Methods

Cell lines, Abs, and radiolabeling. Ramos cells were obtained from the American Type Culture Collection and propagated as described previously (16). While these studies were ongoing, their identity was confirmed by DNA “fingerprinting” done by DSMZ. They were also tested routinely for Mycoplasma contamination, with the Mycotect kit (Invitrogen), and found to be negative. The humanized IgG1 Abs veltuzumab (5), epratuzumab (17), and labetuzumab (hMN-14) were provided by Immunomedics, Inc. Epratuzumab and labetuzumab were conjugated to the metal chelator 1,4,7,10-tetra-azacyclododecane and labeled with $^{90}$Y at a ratio of 5.0 mCi/$^{90}$Y/1.0 mg IgG by methods that have been previously reported in detail (18). The product was prepared on the day of its use with yields usually of >95%. Excess diethylene-triaminepentaacetic acid was added to scavenge any residual unbound $^{90}$Y. Each product was analyzed by instant TLC and size-exclusion high performance liquid chromatography (19). Representative radioconjugates were also tested for immunoreactivity using an anti-idiotype Ab (20) and were >95% reactive. The activity of $^{90}$Y was determined in a Capintec CRC-15R dose calibrator (Capintec). Containers and other conditions were carefully controlled to ensure accurate readings of $^{90}$Y activity (21). The same conjugate was labeled with $^{111}$In, following the same procedure, except with 2.5 mCi/mg IgG.

Ab therapy and biodistribution experiments. All animal experiments were approved by the institutional animal welfare committee. Male BALB/c nude mice were obtained from the National Cancer Institute.
Animal Resources. Typically, groups of 60, 4- to 6-wk-old mice were injected s.c. on the back with 5 to 10×10^6 tumor cells (usually 5×10^6). Tumors grew in 80% to 95% of the mice, appearing consistently in 19 to 26 d. The tumors grew rapidly once they appeared, with a doubling time of 3 d. Because the time of tumor appearance varied over an interval of a week, groups of mice were usually used in two batches, 1 at approximately day 20, and the other 5 d later. On the day of injection, animals bearing tumors >0.1 cm³ and <1.5 cm³ (caliper measured perpendicular L × W × D) were selected and distributed into groups to ensure that the mean tumor size would be approximately the same in all groups.

All Abs were injected iv into the tail vein. In most experiments, veltuzumab was injected on day 0, the day on which tumors were first measured, at doses of up to 1.0 mg, as indicated below. NaY-epratuzumab was injected the following day, together with 0.1 mL of ascites of an irrelevant mouse IgG2a Ab (PK136) to block rapid blood clearance, presumably mediated by the high affinity FcγR CD64 (22). Three additional doses of veltuzumab were injected at weekly intervals, using half the amount given in the initial dose. The first studies used 175 μCi NaY-epratuzumab, but this dose, although sometimes effective, resulted in excessive loss of body weight in a fraction of the animals 2 to 3 wk after injection, in later experiments. Therefore, the dose in subsequent experiments was reduced to 160 μCi. The particular dose used in each experiment is given under Results. Tumor growth was measured once to twice per week. At each time point, mice were observed for signs of morbidity and body weight was determined. Mice with >20% loss of body weight or other signs of morbidity were euthanized. The study was terminated when tumors grew to 3.0 cm³. Ab biodistribution using 111In-epratuzumab was done as described previously (23).

Results

Single agent therapy. Nude mice bearing visible Ramos tumors were injected with either 100 μCi or 175 μCi of NaY-epratuzumab. The mean tumor size at the time of Ab injection was 0.49 cm³ (range, 0.2-1.0 cm³). As shown in Fig. 1C, all of the tumors, large and small, treated with 175 μCi NaY-epratuzumab regressed by day 14, with most having no evidence of tumor at this time. Two to 5 weeks after treatment, the tumors regrew rapidly. In contrast, tumors in untreated animals continued to progress. Most of the tumors in animals receiving 100 μCi of NaY-epratuzumab had a slight delay in tumor growth, but only 2 regressed, and only 1 of these regressed to 0 cm³. Occasionally, untreated tumors regressed spontaneously after reaching a size of >1.0 cm³ (Fig. 1A). The frequency of such regressions never exceeded 20% and, in some experiments, did not occur at all. The tumors that regressed spontaneously in control mice never regrew. The reason for the regressions is unknown.

Figure 1D is a step graph of the same data, showing the time required for tumors to reach a size of 3.0 cm³. Using the log-rank statistical test, the difference between the control group (•) and the 175 μCi group (▼) was not statistically significant because 2 tumors in the control group regressed, but the difference between the 175 μCi group and the 100 μCi group (○) was significant (P < 0.025). Using Fisher’s exact test, at day 27, the difference between the control group and the 175-μCi
group was significant ($P < 0.001$). The body weights of the mice treated with 175 μCi are shown in Fig. 1E. There was a transient loss of body weight (10.7% at day 7), but the mice had largely recovered by day 15. In later studies, some mice injected with 175 μCi had severe, >20%, loss in body weight, and thus, we elected to reduce the $^{90}$Y-epratuzumab dose to 160 μCi for subsequent studies. In some experiments, the time course of tumor regression was examined by measuring tumors twice weekly (data not shown). After the injection of the radiolabeled Ab, the tumors continued to grow for at least 4 days, and sometimes as long as 6 days. By day 11, tumors had become much smaller, and reached a nadir by day 14 to 15 after Ab injection. Thus, the time of dramatic tumor shrinkage occurred between day 6 to 11.

Varying doses of up to 3.0 mg of unconjugated veltuzumab were injected when tumors reached a size of 0.1 to 0.5 cm$^3$. The majority of treated tumors grew at the same rate as control tumors, with no indication of tumor stabilization or regression. Although a subpopulation of tumors regressed after Ab injection, this effect was not statistically significant, partly because of the occasional regression of control tumors, as described above (data not shown; but results of a similar experiment are included in Fig. 2).

**Combination therapy.** Our initial studies were designed to examine a predose of the anti-CD20 IgG before the radio-labeled anti-CD22 in established tumors. Because these tumors progressed rapidly, the unconjugated veltuzumab was administered on day 0, with $^{90}$Y-epratuzumab given the next day. Three additional doses of anti-CD20 IgG were given, each at half the initial dose, at weekly intervals. In the untreated group, in this experiment (Fig. 2A), 12 of 15 tumors progressed to $>$3.0 cm$^3$ within 20 days of Ab injection. Three animals had complete regression of their established tumors with no evidence of regrowth over the 168-day monitoring period, but 1 of these tumors had reached a size of 2.09 cm$^3$ before regressing. Those animals given veltuzumab (hA20) alone (Fig. 2B) or the same dose of an irrelevant $^{90}$Y-labeled IgG (hMN-14 anti–carcinoembryonic antigen; Fig. 2E) failed to control growth more than that seen in the untreated group, with 3 in the veltuzumab-alone group and none in the $^{90}$Y-hMN-14 IgG group being tumor-free at 168 days. Consistent with the previous experiments, $^{90}$Y-epratuzumab alone produced a marked tumor regression in all mice, but the tumors regrew a few weeks later (Fig. 2C). When unconjugated veltuzumab was given with the $^{90}$Y-epratuzumab, 12 of 15 (80%) animals were cured (i.e., no visible tumor) over the 168-day observation period (Fig. 2D). The three tumors that developed grew very slowly. This is shown for 2 of the tumors in Fig. 2D, and the third tumor first appeared at day 140 after the first Ab injection, which is outside the scale of the graph shown. Figure 3 is a step graph of the data, showing the time at which the tumors reached a size of 3.0 cm$^3$. Statistical analysis by the log-rank test showed that the combination treatment significantly improved survival (<3.0 cm$^3$) compared with the other groups ($P < 0.001$).

With the combination effect clearly established, a subsequent study was done to determine if lower doses of veltuzumab would be as effective. The dose of veltuzumab used in the initial injection was 1.0 (as above), 0.3, and 0.1 mg. In all cases, three additional weekly injections at half the initial dose also were administered. All three doses were equally effective, with cure of most or all of the mice treated with both Abs (data not shown). This experiment also included a group treated only with $^{90}$Y-epratuzumab, and in this group, all of the tumors regrew after initial regression, very similarly to the results shown above. We conclude that a total dose of 250 μg (100 μg + 3 × 50 μg weekly) veltuzumab is sufficient to produce the maximum therapeutic effect.

**The effect of veltuzumab on the tumor uptake of $^{111}$In-epratuzumab.** One possible mechanism of action of the veltuzumab is to increase the uptake of $^{90}$Y-epratuzumab in the tumor, which might be by inducing a higher level of expression of the CD22 antigen, or by some other mechanism. In fact, previous in vitro studies suggested that veltuzumab binding induced an increase in CD22 expression (5). To investigate this possibility, an Ab biodistribution experiment was done, in which the distribution of $^{111}$In-epratuzumab was determined with and without injection of 1.0 mg veltuzumab, under exactly the same conditions as used in the therapy experiments. $^{111}$In was used as a surrogate for $^{90}$Y because of the smaller quantification of the $^{111}$In, and because both label the same 1,4,7,10-tetra-azacyclododecane–Ab conjugate. Results shown in Table 1 show that veltuzumab had no effect on the uptake of the $^{111}$In-epratuzumab in either the tumor or any of the normal organs tested. Results are shown only for day 3 after $^{111}$In injections, but essentially very similar results were obtained at day 5. The sizes of the tumors in both groups were very similar, as indicated.

**Discussion**

The results presented show that, in our experimental model, the combination of $^{90}$Y-anti-CD22 Ab and unconjugated anti-CD20 IgG provided a markedly enhanced therapeutic effect, compared with that of either of the Abs alone. $^{90}$Y-epratuzumab alone did have a substantial effect, with essentially all of the tumors regressing to a small size, many to 0 cm$^3$, but all of these tumors regrew a few weeks later. In contrast, veltuzumab alone did not have a substantial effect: there were some indications of therapy in a subpopulation of the mice treated with both Abs (data not shown).
with epratuzumab, but most of the tumors continued growing, unaffected by the Ab injection. This may seem unexpected because epratuzumab was very effective in a Daudi lymphoma model of disseminated disease (5) and has shown high therapeutic activity at relatively low doses in patients with non–Hodgkin’s lymphoma (24). Evidently, therapeutic effects depend on the experimental model used and on factors such as the size of the tumor at the time of therapy and the dose schedule. Furthermore, it is always uncertain how well an experimental model mimics the human situation.

The impressive effect of the 90Y-epratuzumab alone warrants some discussion. Despite the fact that this same conjugate has been widely used in clinical trials (10, 11), there was no previous description of efficacy of this particular conjugate in a mouse xenograft model, although there were reports of effective lymphoma therapy using other radiolabeled anti-CD20 Abs (25). It is interesting to note that the same is true for the radiolabeled Abs to CD20 that were developed into Zevalin and Bexxar, with remarkably little published evidence of effective therapy with radiolabeled anti-CD20 in mouse model systems (26–28). 90Y-epratuzumab was shown to localize specifically to tumor xenografts, although at relatively low levels (29), and the same is true of anti-CD20 Abs (23). In the case of anti-CD20 Abs, the strong therapeutic effect of the unconjugated Ab in the model used by Buchsbaum et al. (30) may have obscured any effect of the radiolabel. The lack of effective therapy in mouse models did not prevent application of these Abs to the clinic because the preclinical models that have been used to evaluate therapy with unconjugated or radiolabeled Abs to CD20, CD22, or other B-lineage antigens have not been predictive of clinical utility, usually underestimating clinical responses. In particular, radiolabeled Abs have seemed to be less active in mouse models than has been shown clinically (27), perhaps partly because of the long path length of the ß-particles used relative to the size of the mouse. In any case, it is interesting to consider why 90Y-epratuzumab had a better therapeutic effect in this study than in previous investigations. The only known difference is that we coinjected an unreactive mouse IgG2a Ab to block Ab binding to Fc receptors. Such binding occurs because of the very low levels of endogenous IgG in nude mice and has major effects on Ab blood clearance and tumor uptake (22). However, there may also be other unknown variables in the experimental conditions.

Given the effect of irrelevant mouse IgG2a on the blood clearance rate of the radiolabeled Abs, it is necessary to consider whether the effect of the unlabeled Abs in these experiments may be due to a similar nonspecific effect on the Ab blood clearance rate. The unlabeled Ab used was in fact a humanized IgG1, which is homologous to mouse IgG2a and binds to the same high-affinity Fc receptor, CD64 (22). Although we have not directly tested the effect of a nonreactive control human IgG1 Ab in this study, there is strong evidence that the effect of the unlabeled Ab is not nonspecific, as follows: (a) As noted, we are already injecting an irrelevant mouse IgG2a to block Fc receptors. The amount injected, 208 µg, is more than twice as much as the dose required to effectively block uptake for at least 3 days (the latest time point tested) in nude mice (31), which provides sufficient time for the radiolabeled Ab to localize to the tumor. Later time points are probably of little significance because most of the 90Y will have decayed. (b) Consistent with this statement, the experiment described in Table 1 shows that the injection of the unlabeled Ab had no effect on tumor uptake of the radiolabeled Ab at day 3 or 5, which indicates that the amount of mouse IgG2a injected was sufficient to block the high-affinity Fc receptor for at least 5 days. (c) In parallel experiments, we have recently shown that 90Y-veltuzumab, like 90Y-epratuzumab, induces temporary tumor regression.3 In this case, four weekly doses of unlabeled veltuzumab again enhanced the therapeutic effect, but only if the first injection was administered 7 days after the radiolabeled Ab, rather than one day before (because injection of the same Ab one day before would directly compete with the radiolabeled Ab). Most importantly, in the current context, unlabeled epratuzumab was also tested, and was unable to enhance the therapeutic effect, demonstrating that the effect of the unlabeled veltuzumab was antigen-specific (because both of these Abs are humanized IgG1).

There were previous reports of effective therapy with unconjugated anti-CD20 Abs in mouse models, but most of the models used are fundamentally different from that used here. The earlier studies generally used nude mice that were further immunosuppressed by sublethal irradiation (30, 32). The tumors did not grow as well if the mice were not irradiated, which implies that there was some natural defense mechanisms that tended to prevent tumor growth. Whatever this mechanism might be, which has not been established, it is likely that it recovers in the weeks after irradiation, and that the action of the Abs may be to enhance this natural defense mechanism. In the current model, no sublethal irradiation or other type of immunosuppression was required. In many other more recent studies (5, 33), therapy was tested on microscopic tumors, in contrast to the established, macroscopic tumors used here. Typically, mice were treated within a few days after tumor cell inoculation. The data obtained from such models may not be applicable to macroscopic tumors, in which the Ab must leave blood vessels and penetrate tumors, and in which effector mechanisms must function within the tumor environment. Isolated tumor cells in the blood, or in interstitial fluid, seem likely to have sufficient effector cells close by to participate in Ab-dependent cellular cytotoxicity, but this is less likely to be the case in a solid tumor, where there may not be sufficient

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**Table 1. Effect of veltuzumab injection on tumor uptake of 111In-epratuzumab**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Control</th>
<th>With veltuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramos tumor</td>
<td>14.75 ± 3.60*</td>
<td>12.76 ± 3.80</td>
</tr>
<tr>
<td>Blood</td>
<td>10.31 ± 1.77</td>
<td>9.93 ± 2.02</td>
</tr>
<tr>
<td>Liver</td>
<td>3.21 ± 1.25</td>
<td>4.06 ± 1.29</td>
</tr>
<tr>
<td>Spleen</td>
<td>3.05 ± 0.73</td>
<td>3.34 ± 0.54</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.21 ± 0.38</td>
<td>3.86 ± 0.70</td>
</tr>
<tr>
<td>Lung</td>
<td>4.50 ± 0.96</td>
<td>4.31 ± 1.25</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.72 ± 0.20</td>
<td>0.99 ± 0.21</td>
</tr>
<tr>
<td>Tumor size (g)</td>
<td>0.63 ± 0.39 g</td>
<td>0.68 ± 0.45 g</td>
</tr>
</tbody>
</table>

*% injected dose/g on day 3 after Ab injection. Values shown are means ± SDs of groups of 7 mice.
†Mass of tumors collected on day 3.
effector cells within the tumor and close to the tumor cells to attack every cell.

The mechanism of action of this type of combined therapy is unknown, and currently under investigation, but some speculation is warranted. As tumors regress, due to irradiation from $^{90}$Y, the tumors must contain large number of macrophages that are phagocytizing and catabolizing the dead tumor cells. The presence of these cells in abundance would seem ideal for an attack via Ab-dependent cellular cytotoxicity on the few remaining viable cells that persist in the tumor. However, one factor that must be considered is that myelosuppression induced by the radiation used may inhibit the function of effector cells. Another possibility is that the unconjugated anti-CD20 IgG alone has been investigated in many experimental models (1, 2, 13, 33, 34), and seems to occur in humans, and application of this combination therapy to the clinic seems warranted. Finally, there is another factor that does not operate in our animal models but would be a major factor in humans: veltuzumab, rituximab, and other anti-CD20 Abs deplete circulating normal B cells in humans (37). This effect in itself would be expected to increase the uptake of radiolabeled anti-CD22 Ab by the tumor because there would be less competition from other antigen-expressing cells.

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Disclosure of Potential Conflicts of Interest

D.M. Goldenberg is employed by, is a director of, and has an ownership interest in Immunomedics, Inc.

Acknowledgments

We thank Rosana B. Michel, Tom Jackson, Dion Yeldell, Angelica Rosario, and Louis Osorio for technical assistance.

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*Clin Cancer Res* 2008;14:6154-6160.

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