Monoclonal antibodies in the treatment of chronic lymphocytic leukemia

M.J. KEATING

Houston TX, USA

The introduction of monoclonal antibodies into the therapeutic arena in chronic lymphocytic leukemia (CLL) has revolutionize the possibility of effective treatment of this indolent condition. The impressive activity of rituximab in the management of lymphoma was obvious early. The usefulness of this antibody in CLL was not as apparent, as in the pivotal clinical trial, small lymphocytic lymphoma (SLL) patients in relapse had a response rate of only 12%.[1] Alemtuzumab when used initially had impressive antitumor activity but very significant toxicity.[2] These two agents are however been built into effective treatment strategies at all ends of the therapeutic spectrum in CLL.

Rituximab

Rituximab is a monoclonal antibody active against CD20, a B-cell specific surface antigen. As opposed to follicular lymphoma, the expression of CD20 on the surface of CLL and SLL cells is dim.[1] Quantitation of the number of surface antigen sites demonstrates a range of 2 – 15,000 CD20 molecules on CLL cells. After the initial disappointing results in the pivotal clinical trial, subsequent studies of conventional dose have also demonstrated a response rate usually in the 10 – 15% partial response rate in salvage therapy.[3] As well as the low antigen density, it was apparent that in SLL the antibody half-life was short and this short half-life was correlated with a low response rate.[1] There was a postulated antigen sink which may be has a consequence of circulating soluble CD20. CD20 is not shed into the plasma but there is clear evidence of a high level of intact CD20 molecules in the plasma of the patients with CLL, perhaps measuring CLL turnover.[4]

In an attempt to get over the short half-life of rituximab, two strategies were developed. The first was to give the conventional dose of 375 mg/m² three times a week rather than once a week. This tripling of the intensity of antibody treatment led to a response rate in the 45 – 50% range.[5]

Another strategy was to increase the dose of rituximab on the weeks 2, 3, and 4 of the conventional once a week for four weeks approach.[6] Day 1 dose was maintained at 375 mg/m². The response rate improved to 40% with clear evidence of a dose response relationship. In this study the fear of severe reactions because of a high circulating white cell counts was lessened as there was only one patient in 40 who had a severe reaction with typical CLL whereas much higher toxicity experiences were noted in patients with prolymphocytic leukemia and mantle lymphoma in leukemic phase. Marginal zone lymphomas had a much lower toxicity likelihood. With association of the dose and a higher response rate, it was clear that rituximab had activity in CLL.

Experimental data has demonstrated that rituximab increases the cytotoxicity of a number of agents including fludarabine, cyclophosphamide, and platinum analogs and anthracyclines.[8] With this in mind, combination programs have been developed. The first of these was to combine fludarabine + rituximab and the Cancer and Leukemia Group B (CALGB)[8] conducted a study comparing fludarabine + rituximab versus fludarabine alone as induction therapy. A significant improvement in CR rate at the end of these six cycles was noted. In this study both arms were consolidated within the additional fours doses of rituximab leading to an overall complete remission on the FR followed by R arm of 47% versus 33% for the F followed by R. There is evidence that patients with a mutated immunoglobulin heavy chain gene (IgVH) had a somewhat higher response rate but longer remission duration.[9] Patients with 6q- and 17p- on FISH analysis had a lower response rate and shorter survival although these patients were few in number.

Various studies have demonstrated that fludarabine combined with cyclophosphamide has a superior response rate and time-to-treatment failure compared to fludarabine alone.[10,11] With this in mind we have conducted both frontline studies and
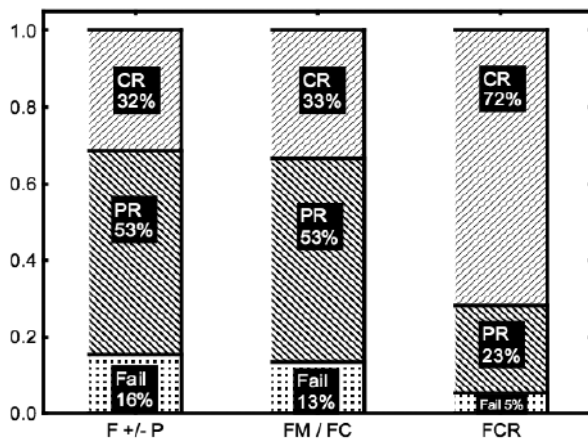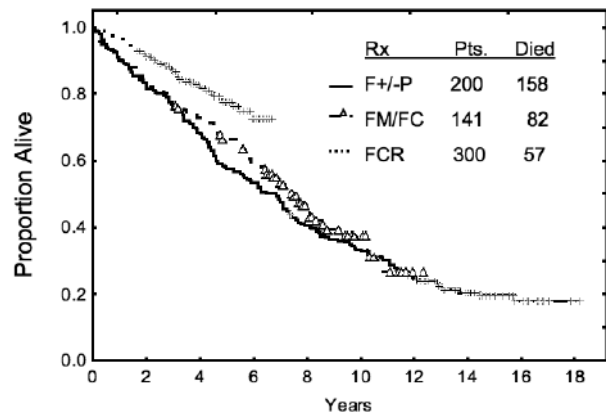
Figure 1. NCIWG responses F +/- P vs. FM/FC vs. FCR.

Figure 2. Survival F +/- P vs. FM/FC vs. FCR.

Table 1. Response (%) in 85 patients.

	N	CR	nPR	PR	OR
Untreated, age >70	14	7	-	79	86
Untreated, ≠↑β2M	35	14	12	54	80
Previously treated	36	6	8	33	47
Total	85	9	8	50	67

salvage studies with FCR in CLL.[12,13] With 300 patients evaluable at the end of the untreated study, the complete remission rate was 72%. The major prognostic factors for response were age, β-2-microglobulin, and Rai stage. The only independent characteristics were β-2-microglobulin and age. The median remission duration for the complete responder patients is >6 years.[14] The addition of R to FC has significantly improved the response rate and survival in patients with frontline CLL (Figure 1 and 2). The eras considered were fludarabine ± prednisone, fludarabine combined with either cyclophosphamide or mitoxantrone and FCR.

The use of rituximab in salvage therapy has been extended to frontline treatment. Hainsworth and colleagues have evaluated frontline therapy with SLL and CLL and obtained an overall response rate of the order of 50 – 60% with a small number of patients achieving complete remission.[15] This is significantly higher than was noted for relapsed patients. In another study in patients with an elevation of their β-2-microglobulin level or symptoms when they were still in early stage with a low tumor burden, a response rate of 80+% was obtained with a number of complete remissions.[16] Thus rituximab appears to work better as a single agent in frontline treatment and in patients with less disease.

A number of biologic agents such as GM-CSF, interferon-α, etc. have the capacity to increase the num-

ber of CD20 antigen sites. Laboratory animal data shows that rituximab + GM-CSF or GCSF will increase the survival of animals.[17] In a lymphoma study in salvage therapy there was a very high complete remission rate obtained with a combination of rituximab + GM-CSF.[18] This has led to a study in CLL of rituximab 375 mg/m² per week for four weeks with GM-CSF at a dose of 250 µg three times a week for eight weeks.[19] The additional four weeks is based on the assumption that rituximab will still be circulating for eight weeks of GM-CSF therapy. Three groups of patients have been entered into this clinical study. Previously untreated patients over the age of 70 years have been entered and have tolerated the treatment well with a high overall response rate. This study is continuing. Patients with early stage disease with a low tumor burden but with a β-2-microglobulin more than 1.5 times normal or symptoms of fatigue, sweats, etc. have been treated with a response rate of 86%. Previously treated patients with CLL have also received rituximab + GM-CSF with a response rate of 47%. With the addition of GM-CSF has increased the response rate to rituximab in phase II clinical trials. Further studies of this potential are warranted (Table 1).

Alemtuzumab

Alemtuzumab (Campath -1H) has been studied for a number of years in CLL with evidence of clear activity but a high incidence of opportunistic infections and infusion related events. The dose of 30 mg three times a week is largely empirical and is not adjusted for surface area and there is little pharmacology data. It appears that the half-life of alemtuzumab is longer in patients with a small tumor load such as those being treated following allogeneic bone marrow transplantation.[20]

In relapse situations, alemtuzumab administered intravenously three times a week for 12–16 weeks is

associated with an overall response rate of approximately 33%.[2] The major side effects are the development of fever and chills with the first 3–5 infusions of alemtuzumab and the development of opportunistic infections, in particular reactivation of cytomegalovirus in weeks 3-6 in approximately 25% of patients.[21] This latter complication is now able to be controlled with prophylactic valgancyclovir.[22] Preemptive therapy rather than prophylactic therapy is also under investigation. The major negative factor in response of CLL to alemtuzumab is the size of the lymph nodes. There is a clear decrease in response to alemtuzumab according to the size of the largest lymph nodes.[2]

Investigators from Sweden have chosen to explore subcutaneous alemtuzumab as frontline therapy for patients with CLL.[23] In 33 patients the response rate was 87% with 19% complete remissions. In this study, after the first few injections subcutaneously many of which were associated with local reactions patients were then able to self-administer the subcutaneous alemtuzumab. The tolerance was much better apart from the local reactions. There were very marked decrease in the number of infusion related incidences. Patients were able to self-administer the agent routinely without untoward side effects. Similar studies are now underway in the United States. A major question which arose is whether alemtuzumab is as effective subcutaneously as compared to intravenous therapy. The German CLL Study Group has conducted a study looking at the use of subcutaneous alemtuzumab in previously treated fludarabine-refractory patients.[24] The response rate which was achieved in this study was very similar to the 33% response rate in patients who were treated in the pivotal clinical trial with fludarabine-refractory disease. Perhaps it appears that these two modes of administration are similar perhaps not identical.

One of the conclusions from animal studies from monoclonal antibodies is that they work best with small tumor burden. Thus alemtuzumab has been explored in the management of residual disease after chemotherapy. This is largely in patients who have residual lymph node disease or bone marrow disease. The bone marrow disease may be >30% lymphocytes from the differential count, persistent nodules in the bone marrow, or a clonal residual population identified by CD5 + CD19 co-expressing cells that are predominantly kappa or lambda expressing. Alemtuzumab is very effective in clearing residual blood and marrow disease and fairly effective in splenic disease. However lymph node enlargement persists in a number of patients. It is clear that patients who are able to have eradication of minimal residual disease have much longer time-to-treatment failure and probably survival.[25,26] Other studies have confirmed this relationship

with an improvement in survival being documented in long comparative clinical trials. In one randomized comparative trial, the time-to-treatment failure of alemtuzumab treated patients compared to controlled demonstrated a much longer time-to-treatment failure but there was a very significant increase in the opportunistic infections that occurred leading to abandonment of the trial.[27] It is quite probable that the reason for the opportunistic infections was the proximity of the consolidation courses to the induction therapy courses. This continues to be an area of active exploration.

Combination antibody therapy

As alemtuzumab is very effective in treating disease in blood, bone marrow, and spleen whereas rituximab is more effective in blood, lymph nodes, and spleen but not very effective in treating disease in the bone marrow, combination approaches have been undertaken. In four-week clinical trials rituximab is given at close to the usual doses and alemtuzumab in the first study twice a week and then the second study a continuous infusion followed by subcutaneous administration.[28,29] In both of these studies there is more than a 50% response rate and with the patients receiving continuous infusion first, the complete remission rate has increased quite markedly. Combination of antibodies appears to have greater cytoreductive capacity. Further clinical trials will need to be undertaken to see if this translates into increased long term control.

Combination chemotherapy and combination immunotherapy

As FC appears to be superior to F, and rituximab and Campath appears to be effective together, the regimen of CFAR has been developed[30]. This has now been given to 120 relapsed/refractory patients. The response rate is 70% with 25% complete remissions. The comparison of the results with CFAR to the FCR regimen showed that the two regimens in salvage therapy were approximately similar with no convincing evidence that the response rate is higher with the addition of alemtuzumab to FCR compared to the FCR alone group.

The role of monoclonal antibodies in allogeneic bone marrow transplantation

The development of the FCR regimen has led to the application of FCR to preparative regimens in non-ablative stem cell transplantation or reduced intensity conditioning transplantation (RIT). FC was effective in allowing engraftment of allogeneic cells in reduced intensity regimens, many of these patients relapsed or died of complications of graft versus host disease (GVHD).[31] With the addition of rituximab in a small

group of patients there has been a marked improvement in survival as well as a reduction in acute GVHD.[32] Chronic GVHD appears not to be as affected as acute GVHD. The addition of alemtuzumab to preparative regimens for matched unrelated donor transplantations is also being investigated. There is evidence of activity of rituximab in patients with acute GVHD as a single agent and the same has been noted with alemtuzumab.

Based on the fact that three different regimens, namely chemoimmunotherapy, use of alemtuzumab for minimal residual disease, and reduced intensity conditioning transplants can all induce MRD negativity, new paradigms for exploration of curative strategies in CLL are underway. An example of such a strategy is illustrated in Figure 3. While the two antibodies described have been noted for a major impact in treatment of CLL, further antibodies are being explored with or without toxins. A human form of CD20 antibody (HuMax) has been explored in CLL and in phase II clinical trials and has had a high response rate.[33] A registration clinical trial for HuMax in CLL in patients who are fludarabine-refractory and refractory to alemtuzumab is being initiated to see if this antibody has activity in such an advanced group of patients. Eframtuzumab which is active against CD22 and rituximab against CD23 have not been explored to a great extent in CLL either alone or combined.

Conclusion

The development of the antibodies, rituximab and alemtuzumab, which seem to have potent activity in different clinical areas has led to a much higher response rate, time-to-treatment failure and probably survival advantage in patients with CLL. Pharmacologically directed therapy needs to be explored so that we can ensure that adequate levels of the monoclonal antibodies are maintained throughout the treatment experience. Each can then be adjusted to get maximum benefit from the effective but extensive therapies.

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