Abstracts of Satellite Symposia

Hoffmann-La Roche, Tuesday, June 1, 1999, Room A, 4:30 p.m.

Mabthera: Future Applications in CD20+ Malignancies

THE ROLE OF MABTHERA® IN MANAGING INDOLENT LYMPHOMA

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The chimeric mAb rituximab (Rituxan™, Mabthera®) is specific for the CD20 antigen that is expressed in high levels on B-cell lymphoma cells. The CD20 antigen does not modulate, is not shed and is nearly an ideal target for immunotherapy. Laboratory studies suggest that the mAb may kill tumour cells through augmented interaction with immune mechanisms of complement-mediated lysis (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) as well as by the direct induction of apoptosis. Clinical trials utilizing 375 mg/m² × 4–8 doses of Mabthera® have demonstrated a 50–60% response rate in patients with relapsed follicular NHL as a single agent (Maloney DG *et al. Blood* 1997; 90: 2188; McLaughlin P *et al. JCO* 1998; 16: 2825). In most patients, side effects are limited to the initial antibody infusions and are usually mild-to-moderate fever and chills, and rarely hypotension or bronchospasm.

The independent activity of this new therapy and its favourable toxicity profile provide the rationale to combine Mabthera® with, or following, conventional therapies. Laboratory studies also support these combinations as Mabthera® may act in additive or synergistic fashion and sensitize tumour cell lines to the effects of chemotherapy. Initial studies (Czuczman, MS *et al. JCO* 1999; 17: 268) demonstrate that Mabthera® may be given safely when combined with standard dose CHOP chemotherapy. The overall response rate was 95%, with a 55% complete response rate. At a median observation time of 29 months, 74% of patients continue in remission. Additional studies utilizing Mabthera® as initial therapy and in combination with, or following, chemotherapy in indolent lymphoma patients are being analyzed.

MABTHERA® IN AGGRESSIVE LYMPHOMA: AN UPDATE ON ITS EFFICACY AND TOXICITY

B. Coiffier. Hospices Civils de Lyon, Pierre-Bénite, France.

MabThera®, a chimeric monoclonal anti-CD20 antibody, has proven efficacy in the treatment of follicular lymphoma patients. Since other B-cell lymphomas also express the CD20 antigen, they may also respond to MabThera® therapy.

Phase II trials have demonstrated the anti-lymphoma efficacy of single agent MabThera® in relapsing diffuse large B-cell lymphoma, relapsing mantle cell lymphoma, *de novo* MCL and post-transplant lymphoproliferative diseases. In relapsing patients, a response rate of 30% to 35% was observed with a schedule of 4 to 8 weeks of MabThera® 375 mg/m²; with a less than 10% CR rate. In untreated MCL, the response rate was 40%, again with less than 10% CR. In post-transplant lymphoproliferative disease, a higher response rate and CR rate was observed, 69% and 54%, respectively. Toxicity in these trials was similar to that described in follicular lymphoma patients.

Phase II trials of the combination of MabThera® with multidrug chemotherapy regimens, particularly CHOP, have shown a higher response rate than with CHOP alone. The toxicity of the combination was not different from that expected with CHOP alone or MabThera® alone.

Currently, large cooperative groups are running prospective randomized trials of CHOP *versus* CHOP plus MabThera® in untreated patients with diffuse large B-cell lymphoma to demonstrate the benefit of the combination in terms of survival or event-free survival. It is too early to present the results of these trials, however, preliminary safety results of the first 100 patients included in the GELA trial will be presented. This trial compares the activity of CHOP, 8 cycles, to CHOP plus MabThera® (375 mg/m²), 8 cycles, in patients older than 60 years with diffuse large B-cell lymphomas.

IN VIVO PURGING AND AUTOGRAFTING OF CD34+ CELLS IN FOLLICULAR AND MANTLE CELL LYMPHOMA

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To overcome the limitations of *ex vivo* bone marrow purging, we have assessed the ability of the anti-CD20 monoclonal antibody MabThera®, in combination with high-dose chemotherapy, to eradicate PCR-detectable disease, and to enable the harvesting of large amounts of uncontaminated circulating progenitor cells (CPCs) in patients with indolent lymphoma. From 4/97 to 12/98, 24 consecutive patients ≤ 60 years of age with a diagnosis of untreated mantle cell lymphoma or of refractory/early relapsed follicular lymphoma entered the study. The first 10 patients and the last 4 patients enrolled received MabThera®, while the middle 10 consecutive patients served as controls. Eligible patients received 2 to 4 courses of standard-dose chemotherapy, followed by one course of high-dose cyclophosphamide plus GM-CSF and/or G-CSF and, three weeks later, by a second high-dose course of cytarabine with CPCs and growth factor infusion. Patients in the MabThera® group received two i.v. doses of the antibody at 375 mg/m² after the last infusion of high-dose cyclophosphamide and cytarabine. CPCs were obtained by leukapheresis when the CD34+ cell count reached ≥ 50/μL. PCR testing occurred on the leukapheresis product after cyclophosphamide administration. For PCR-positive products, additional leukaphereses were performed after cytarabine. If still PCR-positive, *ex vivo* purging with anti-CD19 monoclonal antibody was performed. Twenty patients are evaluable for clinical response. The results of *in vivo* purging are summarized as follows:

	MabThera®	Controls	*p*
% PCR-neg harvests post-CTX	36	20	NS
% PCR-neg harvests p-CTX & AraC	93	40	< 0.01
% PCR-neg harvests p-CTX & AraC	not applic.	80	-
PCR-neg CD34+ × 10^6/kg (median & range)	28.3 (0–75.6)	15.9 (0–53.1)	0.01

The combination of MabThera® and an effective high-dose anti-lymphoma therapy, allowed the harvesting of large amounts of tumour-free progenitor cells in 13 out of 14 evaluable patients, notably including all patients with mantle cell lymphoma. In contrast, only 4 of the 10 patients receiving chemotherapy alone yielded a PCR-negative harvest ($p < 0.01$).

FUTURE PERSPECTIVES: MABTHERA® IN THE NEXT MILLENNIUM

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The availability of effective monoclonal antibodies has revolutionized the management of patients with indolent B-cell malignancies. Those agent in widespread trials include the anti-CD20 antibodies Mabthera®, tositumomab, and IDEC -Y2B8, as well as anti-CD52 CAMPATH. Mabthera® induces responses in around half of the patients with follicular low-grade non-Hodgkin's lymphoma (NHL), with complete remissions seen in 6%. Toxicity has been acceptable; 70 serious infusion-related events and 8 fatalities out of > 20,000 patients, with hypotension, bronchospasm, and severe respiratory distress being the main events seen. Five patients with bulky disease and high circulating tumour cells developed rapid tumour lysis, thromobocytopenia, and mild, reversible electrolyte abnormalities.

Mabthera® has also demonstrated activity in intermediate-grade NHL, mantle cell lymphoma, lymphoplasmacytic NHL, and post-transplant lymphoproliferative disorder. Lower response rates in small lymphocytic NHL and CLL, reflecting the low density of CD20 on the malignant cells, may be overcome by increasing the dose intensity of Mabthera® or by up-regulation of CD20. Mabthera® should also be tested in HIV-associated NHL, multiple myeloma, hairy cells and prolymphocytic leukemia. Very promising results have also been reported in NHL with antibodies conjugated to 131 (tositumomab) and ^{90}Y (IDEC -Y2B8), although the relative role of conjugated and unconjugated antibodies remains to be defined.

Clinical trials are currently defining the role of antibodies in relation to other available therapies. Combining Mabthera® with CHOP, fludarabine-phosphate + mitoxantrone or + cyclophosphamide, interferon-α, high-dose chemotherapy in NHL, and with fludarabine-phosphate in CLL will hopefully produce more effective regimens. The future promise of monoclonal antibodies in indolent NHL is a foundation on which to develop new strategies to achieve the elusive goal of cure.

Ligand Pharmaceuticals, Tuesday, June 1, 1999, Room B, 4:30 p.m.
Two Novel Therapies for the Treatment of Cutaneous T-Cell Lymphoma

CTCL: PROGNOSIS AND QUALITY OF LIFE ISSUES

Reinhard Dummer, Monika Hess, Guenter Burg
Department of Dermatology, University Hospital of Zuerich

Cutaneous T-cell lymphoma (CTCL) comprises a heterogeneous group of cutaneous lymphoproliferative disorders that vary in prognosis. The overall probability of 10-year survival for CTCL is 65%. The probability of survival for all T-cell lymphomas after the first symptoms appear is 90% after 5 years, 52% after 20 years, and 30% after 40 years. Pagetoid reticulosis and lymphomatoid papulosis have a 5-year survival rate of 100%. In mycosis fungoides the average 5-year survival is 70%. In CD30 positive T-cell lymphomas it is around 80%. Besides the type of disease, the extent of skin and organ involvement is essential for the estimation of the survival of the individual patient. The extent of disease can be categorized by the TNM classification. The 10-year survival of CTCL is 97% for T1, 77% for T2, and 50% for T3 and T4. Our data indicate, that the discrimination of prognostic groups is more accurate if a tumor burden index (a weighted skin scoring system) is used to estimate the extent of skin involvement. This indicates that the prognosis for CTCL is excellent in most cases. Due to the chronic morbidity by CTCL, however, quality of life is substantially affected. This is due to emotional, social, and financial concerns as well as physical symptoms such as pain and severe pruritus. Since the available therapeutic options are essentially palliative rather than curative, the positive and negative impacts on quality-of-life are of major importance in these patients.

DAB^{389}IL-2: A NEW FUSION PROTEIN TECHNOLOGY

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Recently, genetic engineering has led to the development of fusion toxins, "designer" targeted effector molecules which combine a targeting ligand, such as a growth factor, with a cytocidal moiety, such as a plant or bacterial toxin. The first genetically constructed family of fusion toxins used diphtheria toxin as the toxophore for receptor binding domain substitution. Diphtheria toxin consists of three domains: an enzymatically active ADP ribosyltransferase domain, a hydrophobic transmembrane domain, and a C-terminal receptor binding domain. Introduction of the enzymatically active domain into the cytosol via receptor-mediated endocytosis results in inhibition of protein synthesis by adenosine diphosphate ribosylation of elongation factor 2. $DAB_{486}IL\text{-}2$, in which the native receptor binding domain of diphtheria toxin was replaced with the full-length interleukin-2 gene, was capable of intoxicating high affinity IL-2 receptor-bearing cells in vitro with an IC_{50} of $10^{-10}M$, whereas cells lacking the full component of the high affinity IL-2 receptor (p55,p75,p64) were relatively resistant (IC_{50} of $10^{-8}M$). Because of a short in vivo half-life of $DAB_{486}IL\text{-}2$, efforts to reengineer the molecule were undertaken, leading to the $DAB_{389}IL\text{-}2$ construct, which had a two to three fold higher Kd than $DAB_{486}IL\text{-}2$ and a longer half-life resulting in a 10-fold increase in potency. Thus far, the clinical activity of both IL-2 chimeric fusion toxins has been similar, with the $DAB_{389}IL\text{-}2$ molecule displaying more favorable pharmacokinetics.

REVIEW OF ONTAK CLINICAL TRIALS IN CUTANEOUS T-CELL LYMPHOMA (CTCL)

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Trials of ONTAK ($DAB_{389}IL\text{-}2$; denileukin diftitox) have been conducted in a variety of diseases, including rheumatoid arthritis, psoriasis, HIV infections, and cancer. The focus of this presentation will be a review of two trials conducted in cancer, in particular those that involved patients with CTCL. Patients in both studies were required to express the interleukin-2 receptor (IL-2r). The first was a phase I dose-escalation trial with eligibility restricted to patients with CTCL, B-cell NHL, or Hodgkin's disease. Trial objectives included evaluating safety, antitumor effects, and determining the MTD. Seventy-three patients entered the trial, 35 of whom had a diagnosis of CTCL. Toxicity felt to be dose-related in this trial included elevations of hepatic transaminases, constitutional symptoms (particularly fatigue), and nausea/vomiting. Overall response rate in this trial was 22% (37% in patients with CTCL). The second trial was a blinded, two-arm parallel group study for patients with advanced CTCL. The objectives of this trial were to evaluate the safety of two dose levels of ONTAK, 9 or 18 $\mu g/kg/day$ for 5 days as an IV rapid infusion every 3 weeks, and determine efficacy and impact on functional state. Seventy-one patients entered this trial, with a median age of 64; 65% of the patients entered were stage IIb or worse. Patients were heavily pretreated with a median of 5 prior therapies. Overall response rate was 30% (23% = low-dose arm, 36% = high-dose arm). The median duration of response for both arms was about 7 months from treatment initiation. A variety of quality of life measures supported the efficacy of the agent for palliation of CTCL. A combined population of patients with lymphoma were treated with ONTAK totals 143, of whom 105 had CTCL. All patients experienced one or more adverse events, which diminished in frequency after the first two courses. ONTAK exhibits the toxicity profile of a biologic response modifier. Infections were common in both trials, probably related to the nature of the patients enrolled. The most common grade 3 or 4 toxicities were constitutional symptoms, seen in 20-30% of patients. Fluid retention and hypotension were observed in 10-27% and reflected the propensity for the drug to cause dehydration secondary to the nausea, vomiting, and anorexia above, but also a vascular leak syndrome in some patients.

ONTAK: OTHER POTENTIAL APPLICATIONS

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Southwest Texas Cancer Institute, San Antonio, Texas

The rational design of new treatment modalities in cancer therapy must emphasize agents with a novel mechanism of action which can overcome tumor resistance, are tumor-cell selective to minimize toxicity, and that address the systemic nature of these diseases. ONTAK ($DAB_{389}IL\text{-}2$; denileukin diftitox) is a ligand fusion-protein which potentially displays these characteristics. The activity of ONTAK in the treatment of cutaneous T-cell lymphoma has established the feasibility of utilizing such a targeted therapeutic in disseminated disease with acceptable toxicity that is not typical of chemotherapeutic approaches. Data from the phase I trial suggest that the definition of activity in other cancer types, including other non-Hodgkin's lymphomas (NHL), is warranted. Three NHL patients in this study responded, two of whom had follicular lymphomas and the third had a primary intermediate-grade NHL that was refractory to chemotherapy and stem cell transplant. This patient has remained in CR over 3 years after treatment with ONTAK. Patients treated to date have had IL-2r-positive tumors, but this remains a very complex clinical issue. The need for a threshold level of receptor expression, the difficulty in obtaining representative tissue, the lack of an assay that accurately reflects high-affinity receptor, and the potential difficulty of observer variability in evaluating the assays should point us toward examining response rates in cancer patients where IL-2r is negative or unknown. The potential to target the high-affinity IL-2r supports the development of this agent in transplantation and in autoimmune diseases. A monoclonal antibody directed against the low-affinity IL-2 receptor has demonstrated activity in solid organ transplant. A similar approach has been attempted in stem cell transplant with monoclonal antibodies to treat or prevent graft vs. host disease. Targeting IL-2r-expressing lymphocytes may also be an effective strategy for the prevention of graft rejection. Finally, autoimmune diseases may be addressed by targeting IL-2r-expressing lymphocytes. ONTAK has been examined in clinical trials of psoriasis and rheumatoid arthritis and has shown promising results. The potential utility in other autoimmune disorders is unknown, but diseases such as systemic lupus, scleroderma, and vasculitis may be effective candidates for such ligand-fusion therapy.

HISTORICAL PERSPECTIVE ON THE USE OF RETINOIDS IN CTCL

Guenter Burg
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Vitamin A and its analogues influence differentiation and proliferation and also may alter immune responses. Limited clinical efficacy of these compounds given alone or as part of a combination therapy has been shown in various types of CTCL, including mycosis fungoides, Sezary syndrome, and prelymphomatous disorders like parapsoriasis en plaque. Compounds used, mostly in small, nonrandomized trials for these diseases, include isotretinoin (13-cis retinoic acid), etretinate, acitretine, and all-trans retinoic acid. Clinical responses have been found despite persistent residual disease with atypical lymphocytes in various compartments. The exact mechanism of action of retinoids in CTCL is unclear and depends on the presence of retinoid receptors on the tumor cells, which is variable in different forms of CTCL. Therapies combining retinoids with PUVA (psoralene ultra violet A) or with interferons may have a synergistic effect, and this warrants confirmation, randomized trials in the future.

DAB_{389}IL-2 PLUS TARGRETIN: A TREATMENT ALGORITHM FOR CUTANEOUS T CELL LYMPHOMA

Madeleine Duvic, MD, MD Anderson Cancer Center, Houston, Texas

Mycosis fungoides, CD4+ epidermotropic CTCL, often arises as indolent, inflammatory chronic and persistent patches and plaques. Conservative and sequential topical therapy patients have the same survival as patients treated with aggressive chemotherapy. Hence, until curative therapy is found, therapies that keep MF in check and prevent progression to more advanced lymphoma may be desirable alternatives to preserve quality of life. Stage IA patients have a normal life span and often receive psoriasis type therapy initially. Targretin gel, a new topical RXR retinoid will resolve MF lesions, reducing dermal T cell infiltrates when used as a single agent. However, it may be even more effective when combined with topical steroids, phototherapy UVB and PUVA, and even with oral Targretin. The gel may also provide a safe adjunctive therapy for individual lesions that are refractory to other agents, including keratodermas. When more than 10% of the body is involved with CTCL or when adenopathy is present (Stage >1B), systemic therapy is indicated. Targretin, has the advantage of easy oral administration, and is extremely effective both for early patients with long-standing extensive plaques, and for late stage patients with Sezary Syndrome or large cell transformation. Monitoring of white count, lipids, and thyroid function is required. Targretin should be tested in combination with interferon or other therapies like photopheresis, PUVA, and methotrexate and for maintenance after TSEBT. ONTAK (denileukin diftitox; DAB_{389}IL-2) is targeted to cells expressing high-affinity IL-2 receptor. ONTAK has given complete or partial remissions in 30% of highly refractory patients with extensive plaques and with disfiguring tumors. Because it is effective in killing T cells that surround dermal vessels, cytokine release may occur and result in capillary leak syndrome. Hence, it will be reserved for more advanced and refractory patients and will require IV administration and monitoring. The use of oral Targretin first to reduce dermal infiltrates prior to ONTAK administration might reduce subsequent side effects imparted by this therapy. With these new, highly effective agents in the armamentarium for the treatment of CTCL, new combination treatment algorithms can be tested to achieve maximal benefit and quality of life for these patients.

TARGRETIN THERAPY FOR CUTANEOUS T-CELL LYMPHOMA

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The clinical experience with Targretin at our center will be reviewed. All patients were seen every 4 weeks for the disease activity assessment. Five target lesions were monitored, an area score was performed, and a CTCL specific health assessment questionnaire was administered. Four patients with refractory plaque CTCL were treated with Targretin gel. All target lesions disappeared after 8 weeks of therapy. There were recurrences in untreated areas. In the followup period, no recurrences of the original target lesions have been observed. One patient has withdrawn from the study. Patients with refractory patch/plaque disease were randomized to a high dose ($300mg/m^2$) vs. low dose ($6.5mg/m^2$) daily oral regimen of Targretin. The two patients randomized to low dose showed disease progression and after 8 weeks were entered into the high-dose arm. There were marked clinical responses in all patients treated. The target lesions showed either complete disappearance or a reduction in the parameters of size, induration, and scale. No new lesions were noted while patients were on high-dose therapy. Self assessments also confirmed the palliative properties of the observed responses. All patients had hypertriglyceridemia despite the concomitant administration of Lipitor 60mg/d. Dose reductions were required to maintain safe lipid levels. Four patients with erythrodermic CTCL were treated with high dose oral therapy. All patients showed rapid (within 2 weeks) improvement of erythroderma and symptoms. The long-term followup will be presented.

Schering Germany, Tuesday, June 1, 1999, Room A, 7:30 p.m.
Molecular Remission of Follicular Lymphoma – the Reality

Follicular lymphoma t(14;18) and rearrangement of bcl2: uses and pitfalls

PWM Johnson (*Southampton, UK*)

The t(14;18)(q23;q32), originally identified by conventional cytogenetics, is closely associated with follicular lymphoma, being detectable in 60-90% of cases depending upon the methodology used. It is also found in a smaller proportion of diffuse large B-cell lymphomas, possibly only those arising by transformation from low-grade disease. The translocation results in the Bcl-2 gene on chromosome 18 being connected to the 5' end of one of the six J_H segments of the immunoglobulin heavy chain locus (IgH) on chromosome 14. The great majority of translocations involve breakpoints in Bcl-2 within two cluster regions - the major breakpoint region (MBR) lying within the 3' untranslated region of the third exon and the minor cluster region (MCR) in an intronic segment at least 20 kilobases 3' to this. Amplification by the polymerase chain reaction (PCR) may be used to detect unique sequences from the malignant clone, thereby allowing small amounts of lymphoma cell nucleic acid to be detected in a background of normal material. The PCR is however prone to give false positive results owing to contamination from previously amplified material, and false negatives in the presence of poor quality nucleic acid or inhibitors of the DNA polymerase enzyme. An additional complication is that the Bcl-2/IgH may also be present in healthy normal individuals at a low level, making the demonstration of sequence identity a requirement for the monitoring of disease in patients with lymphoma.

The association between the detection of the Bcl-2/IgH and the presence of active lymphoma is not straightforward. It has been shown that patients with prolonged remissions following conventional or high dose treatment of follicular lymphoma may have a persistently demonstrable presence of the original translocation clone without developing recurrent disease. There is some data to suggest that failure to remove Bcl-2/IgH bearing cells from autologous bone marrow harvests is associated with earlier recurrent following their use of haemopoietic rescue, although this has not shown in all studies. Patients with PCR-positive bone marrow during follow-up after myeloablative treatment have earlier recurrences, although the relationship is less clear for peripheral blood. Recent studies in patients receiving treatment for follicular lymphoma with fludarabine-based combination chemotherapy or monoclonal antibodies have suggested that in some cases the Bcl-2/IgH may become undetectable in the peripheral blood and bone marrow. The significance of this finding is not yet defined, but 'molecular remission' is an increasingly-used concept in this illness and there is mounting pressure to determine therapy according to PCR results.

The detection of the Bcl-2/IgH by PCR is carried out by a variety of different protocols at different laboratories, making comparison of the results problematic. Variations exist in the PCR primers used, the amplification conditions, the number of cycles and the means of detecting the products. A collaborative study comparing results from 20 different centres in Europe and North America revealed high variation in sensitivity and a disturbing false-positive rate (28%). It is clear that progress needs to be made in standardising the techniques for molecular detection of Bcl-2/IgH cells if decisions regarding therapy are to be based on the results. The emerging data on newer techniques such as the real-time PCR are exciting, as this allows more reliable quantitation than previously. The prospective testing of these techniques in collaborative studies is a high priority in order to make the pursuit of molecular remission a real possibility in the near future.

Detection of minimal residual disease (MRD) by bcl-2 PCR in follicular lymphomas (FL)

F Cabanillas (*U. Texas MD Anderson Cancer Center*)

Most patients with FL achieve a complete response after treatment, but those with stage IV usually relapse due to MRD. The t(14;18) results in rearrangement of the bcl-2 oncogene that constitutes an excellent target for detection by PCR. The PCR assay was used to follow the bcl-2-rearranged cells in peripheral blood (PB) of 116 patients with stages I–IV indolent FL who had a known bcl-2 rearrangement in either the mbr or mcr breakpoints at diagnosis. Patients were treated with various chemotherapy regimens and those with stage IV were maintained on Interferon from 1–2 years post chemotherapy. Landmark analysis was performed at 1 year. After treatment the molecular response rate was 37%, 53%, 56%, and 66% at 3, 6, 9 and 18 months from the start of therapy, respectively. Of 80 patients who attained a molecular CR at some point during the first year of therapy, 76% remain free of recurrent disease at 4 yrs in contrast to molecular non-responders whose projected failure free survival at 4 yrs is 38% (p = .001). We performed multivariate analysis including the classical variables such as B2 microglobulin (B2M), LDH, stage etc. We identified the molecular response and B2M as the only two independent variables associated with FFS. Three prognostic groups emerged: (1) low B2M and molecular responders, (2) low B-2M and nonresponders or high B-2M and responders, and (3) high B-2M and nonresponders. The 4-year FFS of these 3 groups were 86%, 65%, and 23%, respectively. In order to determine if these data also apply to early stage cases, we studied separately those 86 patients with stage I–III previously untreated FL before and after therapy. The following conclusions were reached: 1) In spite of the early stage presentations, most cases had circulating bcl-2 rearranged cells. 2) radiotherapy, although a local treatment, resulted in a relatively high systemic molecular response rate 3) achievement of early molecular response at 3 mos correlated best with clinical outcome. Finally, we examined those patients treated with the new FND regimen (Fludarabine, Novantrone, Dexamethasone) for front line therapy of stage IV FL and found a high rate of molecular remissions at various timepoints during therapy:

Mol. Resp. at 3 mos	Mol. Resp. at 6 mos	Mol. Resp. at 12 mos
16/28 (57%)	17/23 (74%)	13/20 (65%)

Of 33 patients treated with FND and who had a bcl-2 rearranged at diagnosis, 53% are projected to remain NED at 5 years follow-up. When we examined the outcome according to molecular response, we observed that those who had attained a molecular response after 3 mos of FND had a projected 5 yr. failure free survival (FFS) of 78% as contrasted with only 35% for molecular non-responders (p=.05). ***Conclusions***: 1)Molecular response assessed in pb by a PCR technique is along with B2M the most important factor to predict FFS in FL. 2) these data hold for early stage patients with FL. 3) FND is capable of inducing a high molecular response rate in stage IV patients.

Molecular remission following myeloablative therapy

John Apostolidis, Rajnish K Gupta, Demetrios Grenzelias, Peter WM Johnson, Vassiliki I Pappa, Karin E Summers, Ashiq Salam, Keith Adams, Andrew J Norton, John AL Amess, Janet Matthews, Mike Bradburn, T Andrew Lister and Ama ZS Rohatiner

The use of myelo-ablative therapy with autologous haematopoietic progenitor cell support as treatment for follicular lymphoma remains experimental. A major concern has been the risk of re-infusing morphologically undetectable lymphoma cells which may contribute to recurrence. An analysis was therefore conducted to evaluate the long-term results of this approach in patients with follicular lymphoma, treated at St Bartholomew's Hospital with specific emphasis on the prognostic significance of PCR detectable Bcl-2/IgH rearrangements.

Between June 1985 and October 1995, 99 patients with follicular lymphoma received Cyclophosphamide and total body irradiation supported by autologous bone marrow transplantation as consolidation of second or subsequent remission. The bone marrow was treated in-vitro with anti-B cell antibodies and complement. With a median follow up of 5.5 years (range 1.5–12.5 years), 65 patients remain alive, 49 without evidence of recurrence. There were 4 'early' and 10 'late' treatment-related deaths, 7 of the latter being due to secondary myelodysplasia. 38 patients have developed recurrent lymphoma. In 29, the recurrent was overt, in 9 it was detected on surveillance investigations. The projected freedom from recurrence and survival at 5 years are 63% and 69% respectively.

Lymph node biopsy specimens or bone marrow samples were used to determine which patients had a PCR-detectable Bcl-2/IgH rearrangement that was detected in 72 (73%). On multivariate analysis, absence of the Bcl-2/Igh rearrangement at diagnosis and three or fewer treatment episodes prior to high dose therapy, correlated favourably with survival (P = 0.04 and 0.001 respectively).

For patients with a Bcl-2/IgH rearrangement, on univariate and multivariate analysis, absence of the rearrangement (as measured by PCR analysis of bone marrow) during follow up was associated with a significantly lower risk both of recurrence and death (P < 0.001 and 0.02 respectively). The PCR status of the re-infused marrow did not influence outcome.

These results confirm that myelo-ablative therapy can result in prolonged freedom from recurrence in patients with follicular lymphoma. Elimination of cells bearing the Bcl-2/IgH rearrangement appears to be a desirable goal. However, the incidence of secondary myelodysplasia is of increasing concern.

Acknowledgement

We are most grateful to the Medical and Nursing Staff at the Bodley Scott Unit for their expert care. We would also like to thank the Physicians who referred patients for this study.

Molecular remission following antibody therapy

P McLaughlin

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The polymerase chain reaction (PCR) is a powerful tool for the detection of subclinical residual disease, and has been used to monitor those follicular lymphoma patients who have bcl-2 gene rearrangement. Reversion from positive to negative bcl-2 status, either in the peripheral blood or bone marrow, correlates with durability of remission after bone marrow transplantation (Gribben *et al.*, *Blood* 1993; **81:** 3449) or intensive conventional-dose chemotherapy (Lopez-Guillermo *et al.*, *Blood* 1998; **91:** 2955).

In a multicenter trial of the chimeric anti-CD20 monoclonal antibody rituximab, 166 patients were treated, with an overall response rate of 48%, including 6% CR and 42% PR (McLaughlin *et al.*, *JCO* 1998; **16:** 2825). Cells with bcl-2 gene rearrangement were detected pretreatment by PCR in peripheral blood in 55 patients and in the marrow in 52. For those who had serial monitoring, reversion to bcl-2 negative status occurred in the peripheral blood in 19% following the first infusion (10 of 52 patients), 50% (26 of 52) before the fourth infusion, and 62% (26 of 45) by 3 months. In the bone marrow, reversion to negative was seen in 56% (9 of 16) at 3 months.

Since the majority of responders to rituximab were PRs (using very stringent criteria for CR; see Grillo-López *et al.*, *Blood* 1998; **92** suppl 1: 412a), the attainment of 'molecular remission' in the peripheral blood and marrow raises the question that there may be a compartment phenomenon. This issue will be discussed, and placed in perspective with the efficacy of rituximab even in patients with bulky nodal disease (David *et al.*, *Blood* 1998; **92** suppl 1: 414a). The ability of rituximab to result in 'molecular remission' in the peripheral blood and marrow is evidence of its efficacy, and supports its use as an 'in vivo purging' approach prior to peripheral blood stem cell harvesting.

Antibody targeted irradiation and molecular remission

Mark S. Kaminski
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Because of the encouraging results obtained with I-131-Anti-B1 Antibody treatment in low-grade and transformed low-grade B-cell lymphoma patients who had relapsed/refractory disease, a single-center phase II trial in previously untreated, advanced-stage, follicular lymphoma patients was initiated in June 1996 at the University of Michigan. To date, of 57 patients treated, 55 (96%) have achieved either a partial or complete response. As part of this trial, serial PCR of bone marrow and blood for the bcl-2 translocation is being evaluated as a possible marker of molecular remission. Preliminary data has been obtained and reported for patients in whom CD20+ lymphocyte counts have recovered to baseline levels and in whom a maximal clinical response has been ascertained. Of 14 such patients who were PCR positive at baseline, 9 (64%) became PCR negative (8 of 9 being in clinical complete remission) and 7 or these 9 continued to be PCR negative for a mean of greater than 12 months. Data is being compiled on more recently treated patients, but at present the results are not mature enough to determine the clinical implications in terms of relapse-free survival of this mode of molecular monitoring of disease.

SmithKline Beecham, Wednesday, June 2, 1999, Room B, 6:30 p.m.
Emerging Role of Radioimmunotherapy for the Management of Non-Hodgkin's Lymphoma

PROGRESS WITH RADIOIMMUNOTHERAPY FOR NON-HODGKIN'S LYMPHOMA.
Julie M. Vose, MD

Monoclonal antibodies have become a successful treatment for selected patients with non-Hodgkin's lymphoma (NHL). In an attempt to augment the effectiveness of naked antibody preparations, various radio-conjugates, immunotoxins, chemotherapeutic agents, or immune modifiers have been attached to antibodies. The antibody targets most commonly used for the treatment of B-cell NHL include CD20, CD19, and CD22. Antibodies against these targets have been chelated with radio-conjugates such as ^{131}Iodine (^{131}I) or ^{90}Yttrium (^{90}Y) and tested in recent clinical trials. The majority of patients treated on radioimmunotherapy trials have been heavily pretreated patients with indolent NHL or relapsed aggressive NHL. A synopsis of the larger radioimmunotherapy trials with published data and types of patients is outlined in the following table:

Author	Anitbody	Target	Radiolabel	Patients	Response (CR + PR)
White	Anti-Id	Idiotype	^{90}Y	6 Ind, 3 prior CX 3 Agg, 2 prior cx	3/9 (33%)
Knox	Anti-CD20 (B1 or 2B8)	CD20	^{90}Y	17 Ind, 3 prior cx 1 Agg, 3 prior cx	13/18 (72%)
DeNardo	Lym-1	HLA-DR10	^{131}I	6 Ind, 2 prior cx 14 Agg, 3 prior cx	11/20 (55%)
Vose	Anti-CD20 (B1)	CD20	^{131}I	10 Ind/Tx, 2 prior cx 13 Ind/Tx, 3 prior cx 62 Ind/Tx, 4 prior cx	7/10 (70%) 10/13 (77%) 42/62 (68%)
Juweid	LL2	CD22	^{131}I	12 Ind, relapsed 9 Agg, relapsed	2/12 (17%) 4/9 (44%)

Ind = Indolent NHL; Agg = Aggressive NHL; cx = median number of prior chemotherapy regimens received.

Radioimmunotherapy has a theoretical advantage over naked antibody therapy or immunotoxin therapy because the monoclonal antibody conjugated with a radioisotope can have a "crossfire" effect such that antigen-negative tumor cells adjacent to those expressing the target antigen also may be killed. This may enhance the likelihood of tumor sterilization in even bulky disease. Future studies will focus on testing these antibodies in larger patient populations and combining radioimmunotherapy with standard or high-dose chemotherapy and hematopoietic stem cell transplantation.

I-131 Anti-B1 Antibody: Updated Clinical Trial Results. Mark S. Kaminski, MD, University of Michigan Cancer Center.

The initial clinical trial experience with I-131 Anti-B1 Antibody using a nonmyeloablative dosing schedule began in 1990 with a single-center phase I/II study at the University of Michigan. Patients with relapsed/refractory low-grade, transformed low-grade, and intermediate-grade B-cell lymphoma were included. A two-step dosing schedule was established, which included a dosimetric dose followed by a pharmacokinetically adjusted therapeutic dose given approximately 1 week apart. Radiolabeled antibody infusions were immediately preceded by unlabeled Anti-B1 antibody infusions to optimize biodistribution. A maximal tolerated whole-body dose of 75 cGy was established for patients who had not had a history of stem cell autografting. An overall response rate (ORR) of 76% and a complete response (CR) rate of 38% were observed in 53 evaluable patients. The ORR and CR rated in patients with low-grade lymphoma were 92% and 54% and for transformed lymphoma 79% and 50%, respectively. For 15 patients with de novo intermediate-grade lymphoma, the ORR was 47%, but no CRs were achieved. For all responding patients the median duration of response was 8.1 months, and for CRs was 18.6 months. Seven of the original 20 CRs remain disease-free 3 to 6 years after treatment.

Based on these data, a multicenter dosimetry/validation phase II study was conducted in 45 patients with relapsed/refractory low-grade or transformed lymphoma who had progression within 1 year of their last chemotherapy and who had been treated in the past with an anthracycline or anthracenedione-containing regimen. The results confirmed those of the Michigan single-center study with an ORR of 60% and CR rate of 31%. A multicenter phase III study was recently completed in 60 patients with low-grade or transformed lymphoma who had failed to respond or responded for less than 6 months after their last chemotherapy regimen. Using patients as their own controls, the efficacy of the last chemotherapy regimen in terms of response rate and duration was compared to that of I-131 Anti-B1. Whereas only 17 of the 60 patients responded to the last chemotherapy, 39 responded to I-131 Anti-B1. Also, the number of CRs increased from 2 to 10 with I-131 Anti-B1. Whereas 19 patients had equivalent durations of response to the two treatments, 32 had longer response durations with I-131 Anti-B1 versus 9 with chemotherapy. When all studies in low-grade and transformed patients are combined, the median number of prior chemotherapy regimens was 4. The incidence of the development of anti-mouse antibodies is less than 10%.

Another multicenter trial is nearing completion in which patients with relapsed/refractory low-grade or transformed lymphoma are being randomly assigned to treatment with I-131 Anti-B1 or unlabeled anti-B1 (with a crossover to labeled antibody for unlabeled antibody failures). This study is designed to establish the incremental value of the I-131 label.

Finally, the University of Michigan is completing accrual to a trial of I-131 Anti-B1 as frontline treatment for advanced low-grade lymphoma. The response rate is currently 96% and the CR rate is approximately 70%. Molecular remissions for the bcl-2 translocation have been observed, but longer follow-up will be required to establish its value in predicting length of remissions.

These studies indicate that I-131 Anti-B1 Antibody is a safe and effective new treatment for patients with B-cell lymphoma.

Radioimmunotherapy With Autologous Stem Cell Transplantation: Overview of Clinical Experience. Presented by Julie M. Vose, MD. Oliver W. Press, MD, PhD, Janet Eary, MD, Paul Martin, MD, Fred Appelbaum, MD, David Malony, MD, Steven Liu, MD, Wil Nelp, MD, Dana Matthews, MD, Darrell Fisher, PhD and Irwin Bernstein, MD

Radiolabeled monoclonal antibodies targeting B lymphocyte surface antigens provide an approach by which tumoricidal doses of radiation can be selectively delivered to B lymphocytes in patients with relapsed lymphomas. Although antibodies targeting many different cell surface antigens have been tested, anti-CD20 antibodies appear to be particularly advantageous. Preliminary Phase I and II trials with I-131-labeled Anti-B1 (anti-CD20) antibody have demonstrated that myelosuppression is the dose-limiting toxicity.

To assess the maximal potential of I-131-Anti-B-cell Antibodies for treating patients with relapsed B-cell lymphomas, we conducted a series of dose escalation trials in the setting of autologous bone marrow or peripheral blood stem cell support. In an initial Phase I trial of 43 patients, the most favorable antibody biodistributions were obtained when using antibodies directed against the CD20 antigen (eg, anti-B1), with an optimal dose of 2.5 mg/kg. Massive splenomegaly and tumor burdens greater than 500 cc were found to adversely influence antibody biodistributions. Of 19 patients given therapeutic infusions of I-131 antibodies (with bone marrow rescue), 16 achieved complete remissions (84%) and 2 attained partial responses. Cardiopulmonary toxicity was dose limiting at absorbed radiation doses in excess of 27 Gy.

In a subsequent Phase II study, 21 patients were treated with maximally tolerated doses of I-131 Anti-B1 Antibody followed by autologous bone marrow rescue. Eighteen of the 21 treated patients achieved objective responses, including 17 complete remissions.

A recent update of these Phase I and II trials demonstrates that 14 of the 29 patients remain in unmaintained remissions ranging from 27+ to 87+ months after radioimmunotherapy. Late toxicities have been uncommon except for elevated thyroid-stimulating hormone levels found in approximately 60% of patients. We are currently conducting a Phase I/II trial administering high-dose I-131 Anti-B1 Antibody in combination with high-dose cyclophosphamide (100 mg/kg), etoposide (60 mg/kg), and autologous stem cell transplantation in an attempt to improve the percentage of patients who remain continuously disease-free. Of 45 patients enrolled to date, 38 (84%) remain alive and 33 (74%) remain free of progression after a median follow-up of approximately 2 years (range, 1-36 months). Typical transplant toxicities have been observed, including profound myelosuppression and mucositis. Four patients died of progressive lymphoma and three of opportunistic infections.

It is apparent, therefore, that I-131 Anti-CD20 (anti-B1) antibody therapy produces long-lasting remissions in many patients with relapsed B-cell lymphomas when administered at maximally tolerated doses in conjunction with autologous stem cell rescue.

THE FUTURE OF I-131 ANTI-B1 ANTIBODY THERAPY – IS INITIAL TREATMENT AN OPTION? Andrew D. Zelenetz, MD, PhD

I-131 Anti-B1 Antibody is a promising new therapy for the treatment of B-cell lymphomas expressing the CD20 antigen. It is a form of radioimmunotherapy that involves administration of both 131-I-labeled and unlabeled anti-B1 monoclonal antibody. The first dose is a small (5 mCi) tracer dose of I-131, which permits patient-specific dosimetry to be determined. Based on the results of three whole body scans, a therapeutic dose of I-131 is calculated to deliver a 75-cGy dose of whole body irradiation. This approach is well tolerated by patients and has been shown to be highly active (ORR 72%, CR 39%) in both refractory low-grade lymphoma and aggressive transformed lymphomas, with a median response duration in excess of 12 months.

Recent data from Kaminski and colleagues at the University of Michigan have shown significant promise with I-131 Anti-B1 Antibody as initial treatment in low-grade follicular lymphoma (ORR 100%, CR 71%, median response duration not reached). This approach has been generally well tolerated, although human anti-mouse antibodies (HAMA) were detected by laboratory analysis in 41% of patients. No clinically significant adverse reactions (grade 3 / 4) were reported, and only 3% of patients required infusion rate adjustment.

The challenge for future development of I-131 Anti-B1 Antibody therapy is to identify clinical situations in which it will have the greatest impact on the treatment of patients with non-Hodgkin's lymphoma. Therefore, it will be important to determine for which tumors radioimmunotherapy with I-131 Anti-B1 Antibody has significant single agent activity. Trials are planned to determine the activity of this therapy in de novo intermediate grade lymphoma, mantle cell lymphoma, and chronic lymphocytic lymphoma. Given its novel mechanism of action, there is potential for I-131 Anti-B1 Antibody to augment the therapeutic activity of both conventional-dose and high-dose chemotherapy. Because myelosuppression is associated with both conventional chemotherapy and with I-131 Anti-B1 Antibody, trials also are planned to evaluate various combination treatment regimens. In the setting of conventional chemotherapy dosing, clinical trials are planned to determine if radioimmunotherapy following initial therapy can address residual minimal disease. This approach will likely eliminate the problem of HAMA development in untreated patients because chemotherapy will blunt the immune response. In high-dose chemotherapy strategies, the overlapping myelosuppressive toxicity of I-131 Anti-B1 Antibody and chemotherapy is not a limitation to combination use because patients will have autologous stem cells reinfused after therapy. Clinical trials also are ongoing using both low- and high-dose radioimmunotherapy in combination with high-dose chemotherapy to improve the outcome of autologous stem cell transplantation.

The activity of I-131 Anti-B1 Antibody in refractory non-Hodgkin's lymphoma has demonstrated that this represents an important new therapeutic strategy for the treatment of B-cell lymphoma. However, its potential has yet to be realized until it is fully evaluated in other clinical situations and in combination with other forms of therapy.