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Phase I trial of chimeric (human-mouse) monoclonal antibody L6 in patients with non-small-cell lung, colon, and breast cancer

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Abstract. We report a single institution phase I trial of chimeric (mouse-human) monoclonal antibody (chL6) directed against a tumor-associated cell surface antigen expressed in non-small cell lung, colon, and breast cancer. The results of the study were contrasted with a previous trial of murine L6. ChL6 was administered intravenously to 18 patients with advanced cancer as a single, 4–16 infusion in doses ranging from 350 mg/m^2 to 700 mg/m^2. One patient received four weekly doses of 350 mg/m^2. Patients were followed for side effects, localization of antibody to tumor cells, pharmacokinetics and the development of antibodies against chL6. Side effects associated with treatment were chills, fever, and nausea, which lasted 24–48 hours. Platelet count and absolute leukocyte count fell immediately after treatment, but returned to pretreatment levels by day 7. Localization of chL6 to tumor cells in vivo was seen at 350 mg/m^2 and "saturation" at 700 mg/m^2 and 350 mg/m^2 per week × 4. The pharmacokinetics of this antibody appeared similar to its murine analogue. Human antibodies against chL6 were detected in only 4 of 18 patients. These antibodies were directed against murine variable regent and their titers were lower than those occurring in most patients who received murine L6 in an earlier trial. No tumor reductions were seen. Chimeric L6 appears to be a suitable antibody for delivering anti-tumor agents because of its low immunogenicity and favorable in vivo tumor binding characteristics.

Key words: Chimeric – Monoclonal antibody – Phase I trial – Non-small-cell lung cancer – Colon cancer – Breast cancer

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Introduction

Murine monoclonal antibodies (mAb) directed against tumor-associated antigens have many potential uses in cancer diagnosis and therapy [10]. However, most patients develop human anti-mouse antibodies (HAMA) within 2–4 weeks of treatment, which can potentially result in a shortened duration of in vivo binding of mAb to its target antigen and an increase in the rate of clearance [4, 7]. Another disadvantage with murine mAb is their often lower efficiency, as compared to human antibodies, in carrying out the effector functions of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [11, 12, 14]. These two disadvantages have encouraged the development of mouse-human chimeric mAb. These combine the murine variable region of an mAb, which binds to the tumor antigen, and the human constant region, which lacks immunogenicity and can have stronger effector function.

Fell et al. have developed a chimeric antibody (chL6) consisting of the variable region of the murine mAb L6 and the constant region of human IgG1 [5]. Like murine L6, chL6 binds to a 24-kDa protein antigen abundantly expressed at the surface of cells from carcinoma of the colon, lung, breast and ovary [15]. In our previous phase I trial of murine mAb L6, we found good in vivo binding of L6 to tumor as well as some antitumor activity [8]. The binding properties of chL6 are identical to those of murine L6, but it has increased in vitro efficiency in killing tumor cells with human mononuclear cells [5, 14, 15]. As a follow-up to our study with murine L6, we have performed a phase I study of chL6 in patients with advanced carcinoma (lung, colon, or breast), to determine binding characteristics, immunogenicity, toxicity, and pharmacology.

Materials and methods

Chimeric L6. A cell line producing chL6 was made via standard genomic technology as described [5]. Clinical-grade chL6 contained more than 95% protein as chL6 was produced in gram quantities for human use by

Table 1. In vivo localization of chL6 to tumor tissue after intravenous infusion[a]

Patient no.	Dose (mg/m^2)	Day of biopsy	In vivo staining		Antigenic expression	
			Intensity of staining	Cells staining (%)	Intensity of staining	Cells staining (%)
1	35	3	0	0	+4	>75
2	35	3	0	0	+2/+3	>75
3	35	3	0	0	+0/+4	25–75
4	70	3	+1/+3	25–75	+4	>75
		7	+1/+3	25–75	+4	>75
		9	0	0	+4	>75
5	70	5	+3	[b]	+4	[b]
6	70	3	0	0	+4	>75
		7	0	0	+3/+4	[b]
7	140	ND	ND	ND	ND	ND
8	140	8	0	0	+4	>75
9	140	2	0/+3	0	0/+4	[b]
		7	0/+3	0	0/+4	[b]
10	350	3	+3	[b]	+4	[b]
11	350	4	+0/+4	<25	+4	>75
		7	+0/+4	<25	+4	>75
12	350	ND	ND	ND	ND	ND
13	350	2	+3/+4	>75	+4	>75
		6	+1/+3	25–75	+4	>75
14	350	11	0	0	+3	[b]
15	700	2	+3	[b]	+3	[b]
		10	+1/+4	[b]	+2/+4	[b]
		22	0	[b]	+1/+4	>75
16	700	3	+3	25–75	+4	>75
		7	+4	25–75	+4	>75
		14	0	0	+4	>75
17	700	4	+3	[b]	+4	>75
		14	+2	25–75	+4	[b]
18	350	3	+2/+4	[b]	+2/+4	[b]
	×4	11	+2/+4	[b]	+2/+4	[b]
		25	+4	[b]	+4	[b]

[a] Tumors were biopsied on the days noted and directly stained with the peroxidase/antiperoxidase reagents (in vivo staining). The intensity of staining represents the degree of localization of chL6 to tumor in vivo. Antigenic expression represents the maximal degree of in vitro staining with the addition of excess chL6. A comparison of these two values gives an indication of the degree of in vivo saturation. ND, not done

[b] Not evaluable because of the poor quality or small size of the biopsied tissue

InVitron Corporation (St. Louis, Mo.), under FDA established criteria. To maintain chL6 in the monomeric form, the mAb was formulated in 0.5 M NaCl and 0.05 M sodium phosphate pH 7.2.

PAP staining. A modification of the Sternberger peroxidase/antiperoxidase (PAP) technique [6, 18] was used on acetone-fixed frozen sections to assay patient tumor samples. To determine if the expression of the L6 antigen was changed by exposure to chL6 in vivo, the degree of tumor staining by excess or "saturating" amounts of chL6 added in vitro was compared before and after treatment. All slides were coded and read blind by a single observer (I. H.). The degree of staining of individual cells was graded between 1+ (very weak) and 4+ (very strong). Heterogeneity was graded by examining different areas of the biopsy specimen for variability in PAP staining of individual cells. Grading was done by assessing both the intensity of staining (+1, +2, +3, or +4) and estimating the percentage of cell staining at that intensity (<25%, 25% to 75%, or >75%).

Assay for in-vivo antibody binding. Biopsies of accessible tumor were taken within 96 h of the completion of chL6 infusion and at intervals thereafter. Half was placed in formalin while the other half was frozen. To evaluate the degree of in vivo binding of chL6 to tumor cells, sections were exposed to an anti-idiotypic mAb, as previously described, without the addition of chL6 [8]. In parallel, sections of the same biopsies were incubated with excess chL6 before staining. A comparison of these two sections gave an estimate of the degree of in vivo binding to target antigen.

Assay for mAb chL6 binding to platelets and mononuclear cells. The binding of chL6 to platelets and mononuclear cells in peripheral blood was studied by fluorescent antibody staining. Platelets and mononuclear cells were isolated from peripheral blood by centrifugation and Monopoly resolving media (Ficoll Hypaque, Flow Laboratories). The fractions containing platelets and mononuclear cells were mixed with purified murine L6 and fluorescein-isothiocyanate-labeled goat anti-mouse IgG

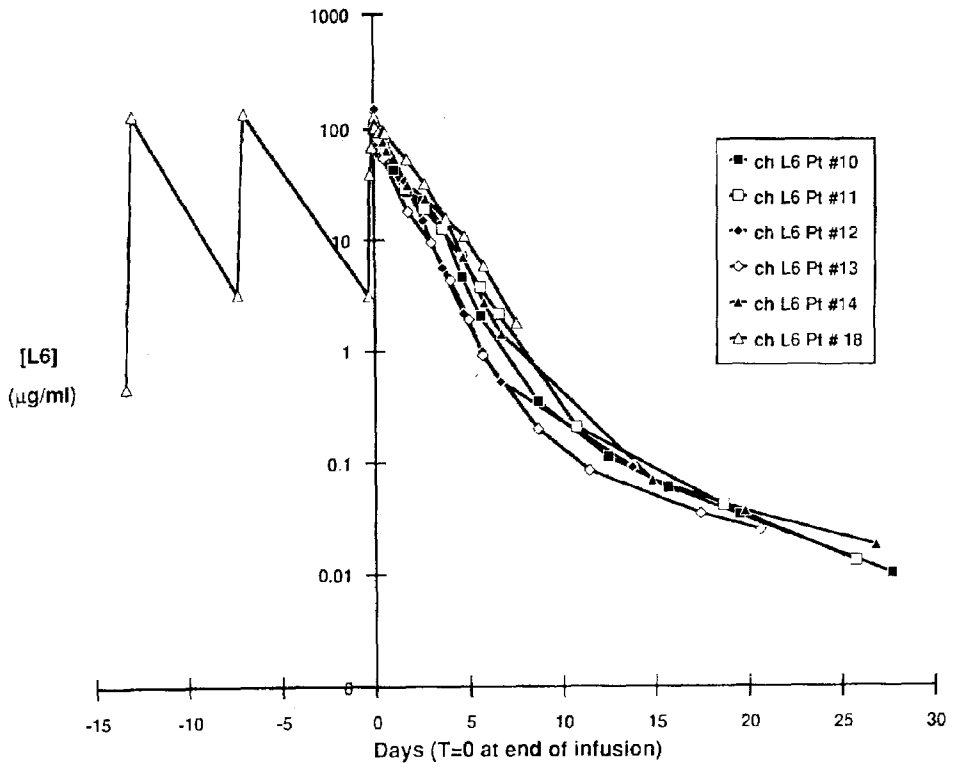

Fig. 1. Disappearance of chL6 from the serum of patients 10–14 who received a single dose of chL6 350 mg/m^2 i. v. over 8 hours on day 0. Serum samples were collected at timed intervals and analyzed for chL6. Results are expressed as µg chL6/ml serum. Patient 18 received four weekly 8-h infusions of chL6 at a dose of 350 mg/m^2 week^{-1} (first week of treatment results not shown). The disappearance curve of chL6 from the fourth week of treatment is co-plotted with patients 10–14 showing an identical disappearance curve

as the second step. Negative controls included no mouse antibody and an isotype-matched irrelevant antibody. The positive control was an anti-CD9 antibody (FMC8, Seralab, Sussex, England) known to bind to platelets.

Assay for mAb chL6 in patient serum. A capture enzyme-linked immunoadsorbent assay (ELISA) was used with two anti-idiotypic antibodies against chL6 to measure chL6 in patient serum [8]. Briefly, 100–200 ng anti-idiotypic antibody was plated per well in a 96-well Immulon plate (Dynatech Laboratories, Chantilly, Va.). After overnight incubation at 4° C, the plate was treated for 1 h with a blocking agent consisting of specimen diluent (Genetics Systems, Seattle, Wa.). Patient sera were diluted in specimen diluent at dilutions ranging from 1 : 2 to more than 1 : 1000 so that the absorbance values fell within the linear range of the chL6 standard curve. chL6 standards 50 µl/well and diluted serum samples were incubated at 4° C overnight. The plate was then washed and 100 µl biotinylated antibody no. 13 was added, incubated for 1 h, washed, and incubated for 30 min with an avidin/horseradish-peroxidase complex (Vectastain, Vector Laboratories, Burlingame, Calif.). A sample containing 100 µl/3,3′, 5,5′-tetramethylbenzidine chromogen was added and incubated for 15 min. The reaction was stopped by the addition of 100 µl 1.5 M sulfuric acid. Plates were read on a Biotek microplate reader in the dual-channel mode (Biotek, Wincoski, Vt.). Linear regression analysis was performed on the chL6 standard curve and chL6 serum concentration was calculated from the curve.

Assay for antibodies directed against chL6. A "double-antigen" ELISA was used to monitor the development of antibodies to chL6 in patient serum. Ninety-six-well Immunlon II plates were coated with 100 µl 300 ng/ml chL6 antibody, the plates were blocked with specimen diluent (Genetic Systems) and then washed. Patient sera were diluted in two-fold dilutions starting at 1 : 2 and 100-µl samples were added to the wells. After an overnight incubation at 4° C, the plates were washed and 100 µl 1 µg/ml biotinylated chL6 in conjugate diluent (Genetic Systems) was added and incubated 4 h at room temperature. After another wash, 100 µl Vectastain was added for 30 min, the plates were washed again and chromogen was added. The assay can detect less than 10 ng/ml of most monoclonal antibodies. We considered a sample positive if it yielded a signal-to-background ratio greater than 5.

Assay for ADCC. Assays for ADCC were carried out using published techniques [14, 15]. Natural killer (NK) cell activity was roughly estimated as the killing of target cells in the absence of added mAb, although it is realized that a minor part of this killing can be mediated by effectors other than NK cells.

Patients. Eligibility criteria included (a) a histological diagnosis of breast, colon, or non-small-cell lung cancer, (b) measurable disease, (c) at least one discrete metastatic site available for biopsy, (d) disease not curable by current treatment modalities, (e) no anticancer treatment within 4 weeks of antibody therapy, (f) no brain metastases, (g) a Karnofsky performance status of 60 or greater, (h) adequate renal (creatinine $\leq$1.8 mg/dl), hematological (white blood cells $\geq$3000 µl, platelets $\geq$100 000/µl), and hepatic function (bilirubin $\leq$1.5 mg/dl) and (i) no prior treatment with murine or chimeric antibodies or fragments.

Treatment plan. The dose levels of chL6 administered were chosen to correspond to the total dose of murine mAb L6 given in our previous phase I trial [8]. The single-dose escalation scheme is shown in Table 1. To explore a multiple-dose treatment schedule, patient 18 received a weekly dose of 350 mg/m^2 for 4 weeks.

chL6 was administered as an infusion in 2.5% human serum albumin. To insure that chL6 remained in solution as a monomer, the solution used required a minimum of 100 mequiv Na^+/l. Since the higher doses of chL6 resulted in a significant NaCl and volume load, we limited the maximum infusion rate to 125 ml/h. This resulted in infusion durations of 4 h (35 mg/m^2) to 16 h (700 mg/m^2). Patients were hospitalized for antibody infusion with an additional 24 h for monitoring.

After discharge the patients were seen three times a week for 2 weeks, then weekly for 6 weeks. Prior to treatment, immediately after the infusion of chL6 and at each visit to the clinic, blood samples were drawn for a complete blood cell count with differential counting, reticulocytes and platelets, serum liver enzymes, calcium, bilirubin, glucose, electrolytes, urea nitrogen, creatinine, serum amylase, and determination of the third and fourth components of complement as detected by radioimmunodiffusion. Serum samples for the determination of HAMA were collected before treatment and at weekly intervals thereafter. To determine the peak serum concentration and the clearance of chL6 from plasma, timed serum samples were collected immediately before and

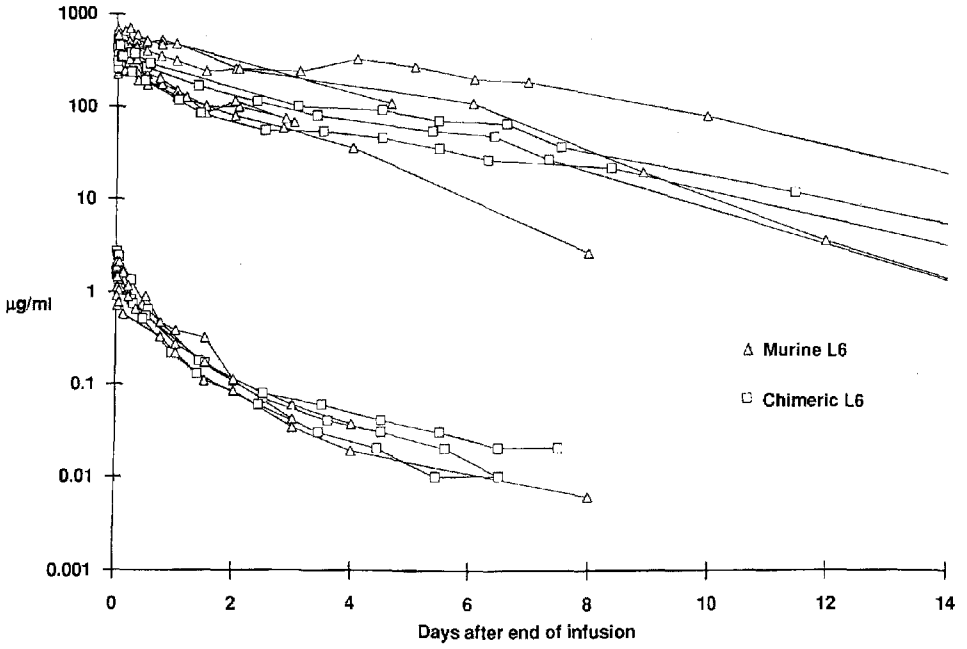

Fig. 2. Comparison of clearance of high and low dose of murine L6 and chL6. The disappearance curves are co-plotted for doses resulting in similar serum concentrations at $t = 0$. The doses compared are: low dose: L6, 20 mg m^{-2} day^{-1} and chL6, 35 mg/m^2; high dose: L6, 400 mg m^{-2} day^{-1} and chL6, 400 mg/m^2

after treatment. In patient 18, serum samples were taken before and after each infusion and at timed intervals after the last infusion on the 4th week of treatment.

Results

Between June 1989 and July 1990, 18 patients were selected for the study: 9 had breast cancer, 8 had colon cancer, and 1 had non-small-cell lung cancer. Their mean age was 57 years with a range of 32–72 years; 13 patients were women and 5 were men. The mean Karnofsky performance status was 80% with a range of 70%–100%. At entry, 1 patient had thrombocytopenia (77000/µl) and one had an elevated creatinine (2.0 mg/dl).

In vivo localization of chL6

To evaluate the in vivo localization of chL6 to tumor cells, tumor biopsies were taken 3 days after treatment and at intervals thereafter. Table 1 shows the degree of localization by evaluating the intensity of staining of individual cells and the percentage of cells staining. Consistent detection of chL6 on the surface of tumor cells was first seen in patients who had received 350 mg/m^2. In patients receiving 700 mg/m^2, saturation was approached. In vivo staining not enhanced by the addition of excess chL6, representing full saturation, was seen in the single patient receiving 350 mg/m^2 $week^{-1}$ after the second week of treatment.

In three patients (15, 16, 17) in whom serial biopsies could be taken, the duration of in vivo binding appeared to be greater than 1 week. We found no evidence of antigen loss as a result of treatment since, in those patients who had pretreatment biopsies, the maximal intensity of staining was similar before and after antibody infusion (data not shown).

In parallel with the immunochemistry studies, tissue was processed for routine histology. There was no convincing evidence of a lymphocytic infiltrate or of tumor necrosis compared to pretreatment biopsies.

There was no in vitro evidence of L6 binding to platelets or mononuclear cells. The binding ratio of the linear fluorescent equivalents of the sample to the negative control was in the range 1.3–1.0 for L6, 1.0–0.9 for the irrelevant antibodies and 20–15 for the specific antibody. This indicates that platelets and lymphocytes do not express the L6 antigen.

Pharmacokinetics

Figure 1 illustrates the disappearance of chL6 from the serum for 5 patients receiving single infusions of 350 mg/m^2 chL6 and for the single patient receiving 350 mg m^{-2} $week^{-1}$ for 4 weeks. The data illustrate the biphasic nature of the clearance curve and also show that the clearance was not substantially altered after four weekly infusions of chL6. The serum half-life ranged from 2.27 days to 4.55 days over the doses studied. Figure 2 compares the serum clearance of murine L6 in patients receiving murine L6 (previously published in [8]) to that of the patients receiving chL6. Figure 2 compares doses of each mAb that resulted in similar maximal serum concentrations, both at low and high doses of mAb. Although the difference in treatment protocol complicates the interpretation, the rates of clearance of murine and chL6 appear to be indistinguishable.

Human antibodies directed against chL6

Four patients developed antibodies to chL6. Time to development of the first titer was 1, 2, 6 and 11 weeks. In the patient with the highest antibody titers, the human

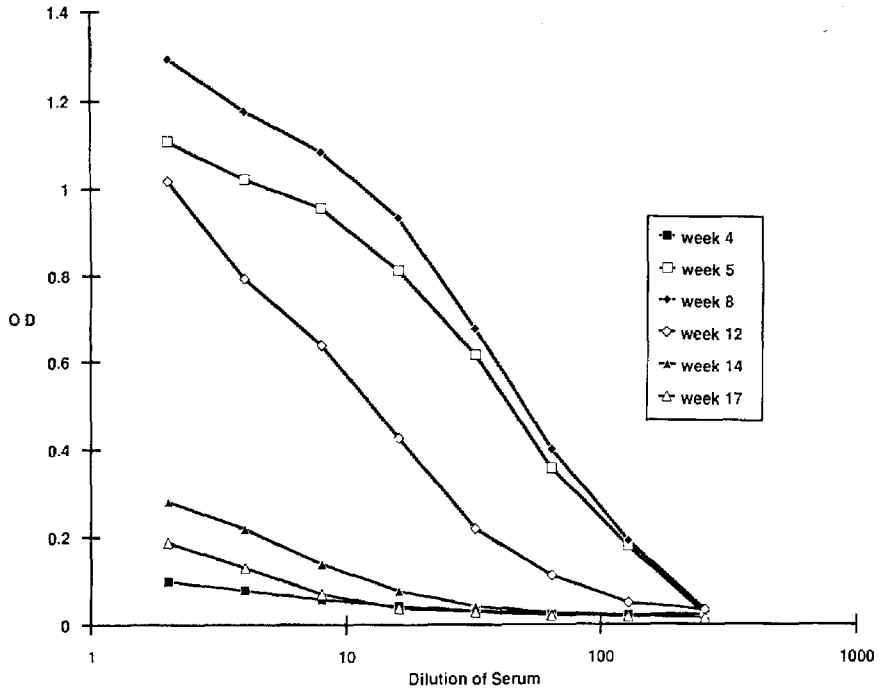

Fig. 3. Anti-chL6 antibody titers in patient no. 9 between week 4 (when antibodies were first detected) and week 17. Result shows the anti-chL6 antibody titer rapidly reaching a peak at week 8, but falling by week 14

Table 2. Number of patients in which toxicity occurred within 48 h of chL6 infusion (SWOG criteria)

Toxicity	SWOG grade	No. of patients experiencing toxicity after a dose (mg/m^2) of:				
		35 (3)	70 (3)	140 (3)	350 (5)	700 (3)
Fever	0–1	–	–	–	–	–
	2–3	3	2	3	3	3
Chills	0–1	2	1	1	2	–
	2–3	1	1	2	2	2
Nausea + vomiting	0–1	1	2	2	2	2
	2–3	–	–	–	1	–
Headache	0–1	1	1	–	1	–
	2–3	–	–	2	1	1
Hypo-tension	0–1	–	–	1	2	1
	2–3	–	1	–	1	–
Tumor pain		–	–	2	–	–

[a] *n*

antibody response appeared to be directed against the murine variable portion of chL6. The cross-linking of chL6 was not blocked by either a murine IgG2a or a human Ig1 control antibody, while binding was completely blocked by both murine L6 (an IgG2a) and chL6, showing that the antibodies were directed to the variable region. In the other patients, the titer of antibody response was too low for a detailed analysis.

The antibody responses seen in these 4 patients were quantitatively weaker (generally 1/10 to 1/100 in titer) than those observed in patients receiving murine L6 [15]. Furthermore, in contrast to our observations of the HAMA response to murine L6, in which HAMA titers rose to a plateau and remained stable for many weeks, in 1 patient for whom late serum samples were available, HAMA titers to chL6 tended to fall close to baseline a few weeks after achieving their peak (Fig. 3).

ADCC

Peripheral blood mononuclear cells were harvested prior to treatment and 7 days after treatment. ADCC was evaluated by a ^{51}Cr-release assay at a chL6 concentration of 2.6 μg/ml and an effector-to-target cell ratio of 100:1. Prior to treatment, mean total target cell lysis (lymphocytes plus chL6) was 42.8% and natural killer cell (NK) activity (lymphocytes alone) was 7.5%. Total target cell lysis on day 7 was less than that prior to treatment falling to 16.3% and NK to 2.0%.

Clinical observations

In general, chL6 was well-tolerated. Side-effects occurring during treatment and within the first 48 h were graded by Southwest Oncology Group criteria and are noted in Table 2. Most patients developed chills and fever during and immediately after the antibody infusion, which resolved within 48 h of treatment. A fall in platelets was noted in the immediate post-treatment blood sample (mean 274×10^2/ml to mean 181×10^3/ml) with a return to baseline by day 7. The peripheral blood absolute lymphocyte count also fell within the first 24 h after treatment was completed (pretreatment: mean 1.1, posttreatment: mean 0.4). This decrease did not appear to be dose-dependent. Lymphocyte counts returned to pretreatment levels within 7 days (mean 1.0). In addition, there was a rapid decrease in the serum concentration of the third and fourth components of complement in all patients. Complement concentrations fell within 24 h of administration of chL6 and

Table 3. Serum complement components C3 and C4 after a single intravenous infusion of chL6[a]

Dose level	Median (range) of C3 (mg/dl)		Median (range) of C4 (mg/dl)	
(mg/m^2)	Baseline	Nadir	Baseline	Nadir
35	88 (84–124)	88 (52–123)	26 (17–33)	17 (14–30)
70	132 (65–155)	118 (94–119)	29 (5–48)	17 (14–29)
140	110 (95–121)	76 (66– 96)	27 (8–24)	7 (6– 8)
350	125 (112–179)	103 (79–128)	30 (26–44)	13 (5–43)
700	130 (112–139)	74 (51– 75)	29 (27–36)	<8 (5–<8)

[a] Serum was collected prior to treatment, immediately after the infusion of chL6 and three times a week for 2 weeks

returned to normal within 7–14 days. This fall was dose-related with the higher doses of chL6 inducing a more profound and persistent fall (Table 3). There were no other changes in the other laboratory parameters followed. There was no evidence that infusion of chL6 influenced the clinical course. No tumor regressions were seen.

Discussion

Chimeric antibodies have been developed to circumvent several clinical disadvantages of murine antibodies, i.e., a rapid serum clearance, the development of HAMA, and less than optimal functional activity with human complement and effector cells. This trial was designed to investigate whether chL6 showed an improvement over the previously studied murine L6 with respect to these characteristics.

We saw strong in vivo binding of chL6 to tumor at a single dose of 350 mg/m^2, which approached saturation at a single dose of 700 mg/m^2, similar to that observed with murine L6 when given at a dose of 400 mg m^{-2} day^{-1} for 7 days [8]. In the limited number of patients having serial biopsies, the duration of binding of chL6 to antigen-positive tumor cells appeared to be greater than 1 week, similar to that observed with murine L6. This again suggests that chL6 will be suitable for therapies that require prolonged in vivo localization of an agent to tumor, e.g. for targeting of a radioisotope.

As opposed to findings with other chimeric antibodies and their murine analogues [17], the pharmacokinetics of chL6 was similar to that of murine L6 when the effect of increasing dose is taken into account. These findings suggest that in the absence of antibodies directed against the injected antibody the rate of elimination of both murine and chL6 from serum is similar. Although these findings are unexpected, they serve to illustrate that the mechanisms determining clearance of mAb are unknown and are not solely dependent on the isotype of the antibody.

The relationship between dose administered and serum disappearance suggests a "sink" phenomenon, i.e. the existence of a compartment that rapidly binds the L6 mAb and results in a rapid clearance. Once this compartment is "filled", the serum half-life increases and binding to tumor cells become more prominent. Studies performed thus far with radiolabeled chimeric and murine L6 have supported this interpretation [2]. While specific binding of mAb L6 to a large number of normal cells with low antigen density may explain the sink effect, the mechanisms of mAb clearance are complex and not easily generalized. Ongoing trials with radiolabeled trace amounts of chL6, along with unlabeled chL6, will prove useful [3].

As expected, the induction of antibodies directed against chL6 was much less frequent and of different character from that seen with murine L6. In our previous phase I trial with murine L6, the majority of the patients initially developed HAMA, first against the constant region and later also against the variable region of the murine antibody [8]. Although we did detect antibodies in 4 patients receiving chL6, they occurred at a later time (mean 5.5 weeks), in lower titers and less frequently than in patients receiving murine L6. In the patient with the highest titer of antibodies (enough for analysis) we were able to show that during the peak response all antibody was directed to the murine variable region of the antibody. This response was transitory and fell to nearly undetectable levels by week 17.

One may speculate that the lower incidence of antibodies against chL6 was due to the absence of the highly immunogenic murine constant region of murine L6, which may act as a "carrier". Since the development of antibodies to murine antitumor mAb, particularly to their idiotypes, has been suggested to play a role in the antitumor responses occasionally seen in patients receiving murine antibodies [13] including murine L6, the lesser immunogenicity of chL6 may decrease the probability that unmodified chL6 will show clinical efficacy.

In addition to inducing anti-idiotypic antibodies, it is possible that the murine component may play a role in the clinical response via other mechanisms. The broader HAMA response to the mAb constant region may, for example, allow the murine mAb, while residing on the surface of the tumor cells, to act as a "surrogate" tumor antigen for either a T-cell or humoral response.

The low incidence, titer, and late occurrence of antibodies directed against chL6 suggests that repeated treatments may be possible. Thus far 1 patient has been treated on a weekly $\times 4$ schedule. No antibodies to chL6 were detected, and the serum clearance of chL6 after the fourth dose was similar to that after the first one. Strong in vivo binding of chL6 to tumor was also maintained. If this finding is confirmed in more patients, chL6 holds promise for the delivery of anticancer agents to tumors since repeated therapy is likely to be necessary to obtain clinical responses.

There was no evidence of an antitumor response in any of the patients receiving chL6. This was in the face of

excellent localization of antibody to tumor with a decrease in serum complement and lymphocyte counts suggesting that complement and lymphocytes had been sequestered outside the bloodstream. Since tumor biopsies showed no influx of lymphocytes or macrophages, we must conclude that cells able to effect ADCC did not localize preferentially to chL6-coated cells.

Although we and others have shown definitive clinical responses in a few patients treated with antitumor mAb, most of these responses have occurred at least 6–8 weeks after treatment suggesting that they were not caused by mAb-directed tumor cell killing via ADCC or CDC, but were rather the result of an activated host response [8, 13, 19]. It remains unclear whether ADCC and/or CDC can be activated at tumor sites in human patients and, if so, whether these mechanisms are sufficiently potent to cause tumor lysis leading to a clinical response. Many of the currently available lymphokines and growth factors, such as interleukin-2 and macrophage-colony-stimulating factor can augment certain effector cell functions, and clinical trials of these factors in combination with mAb may be appropriate [1, 9, 16]. It is likely, however, that the primary use of antitumor antibodies will not be as unmodified molecules but for the targeting of conjugated anticancer agents.

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