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Research Article

Pharmacokinetics of a Mouse/Human Chimeric Monoclonal Antibody (C-17-1A) in Metastatic Adenocarcinoma Patients

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The pharmacokinetic characteristics of a mouse/human chimeric monoclonal antibody (C-17-1A) were determined in 10 patients with metastatic adenocarcinoma following the administration of either 10-mg or 40-mg infusions as a single or multiple dose. The administration of single 10-mg ($n = 5$) and 40-mg ($n = 5$) doses infused over 1 hr resulted in mean apparent steady-state distribution volumes of 4.13 ± 0.97 and 5.16 ± 1.92 liters, respectively, indicating that C-17-1A appears to distribute throughout the vascular compartment and into limited extracellular fluid volume. The disposition of C-17-1A was adequately characterized using a two-compartment open model with mean distribution half-lives of 15.8 and 18.5 hr and mean elimination half-lives of 90.0 and 97.6 hr for the 10- and 40-mg groups, respectively. A linear relationship was observed between AUC and dose (μg/kg). The clearance of C-17-1A was correlated linearly with total Ig, IgG, and tumor size. Multiple administration of either 10-mg ($n = 3$) or 40-mg ($n = 3$) doses of C-17-1A infused over 1 hr every 14 days for a total of three doses resulted in superimposable mean serum concentration versus time data and consistent mean pharmacokinetic characteristics. These data indicate that C-17-1A exhibits linear, nonsaturable distribution and elimination characteristics in man over the dose range studied (i.e., 130 to 880 μg/kg). The multiple-dose pharmacokinetics of C-17-1A were predictable, indicating a lack of an antibody response to C-17-1A over a period of 42 days. The clearance of C-17-1A exhibited large interindividual variability with significant correlations to circulating IgG levels and tumor size.

KEY WORDS: chimeric mouse/human monoclonal antibody; metastatic adenocarcinoma; single-dose pharmacokinetics; multiple-dose pharmacokinetics.

INTRODUCTION

Native and conjugated murine monoclonal antibodies have been used successfully in a number of therapeutic situations in man including the treatment of drug toxicity (1), organ transplantation (2), bone marrow transplantation (3), cancer (4), and radioimmunoimaging (5). The utility of native and conjugated murine monoclonal antibodies is limited by the natural activity of the antibody and the development of side effects including anaphylaxis and human anti-mouse antibody (HAMA) production (6). Cancer treatment with murine monoclonal antibodies has been limited by moderate pharmacologic activity, immunogenicity, and short circulating half-lives. The immunogenicity of murine monoclonal antibodies has restricted their use to single-dose and/or multiple-dose administration over a short period of time. The recent ability to clone genetic constructs composed of the variable regions of mouse monoclonal antibodies and the constant region of human immunoglobulins has led to the development of chimeric mouse/human monoclonal antibodies with desirable specificity and pharmacologic activity (7). The primary therapeutic advantages of chimeric antibodies lie in their potential to exhibit reduced immunogenicity, longer circulating half-lives, and enhanced pharmacologic activity (7,8).

This report describes, in greater detail, the single- and multiple-dose pharmacokinetics of a mouse/human chimeric monoclonal antibody (C-17-1A), observed during clinical investigations of its immunogenicity, efficacy, and kinetics by LoBuglio *et al.* (9). C-17-1A is composed of the variable regions from the extensively studied (10,14) 17-1A murine monoclonal antibody (M-17-1A) with specificity to a 41-kD glycoprotein antigen present on the surface of gastrointestinal adenocarcinoma cells and the constant regions from human IgG1 heavy and K light chains (15). C-17-1A retains the tumor antigen specificity and human effector cell recognition of M-17-1A (15). The specific objectives of this report are (i) to determine whether C-17-1A exhibited linear single-dose pharmacokinetics, (ii) to evaluate any changes in C-17-1A pharmacokinetic parameters during multiple-dose adminis-

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tration, and (iii) to identify correlations, if any, between C-17-1A pharmacokinetic parameters and selected demographic characteristics.

MATERIALS AND METHODS

Patient Selection

Ten patients (six male, four female) with metastatic adenocarcinoma of the colon were recruited through the Comprehensive Cancer Center of the University of Alabama at Birmingham. The protocol was conducted in accordance with an Investigational New Drug Application submitted to the Food and Drug Administration. Each patient provided informed consent in accordance with the regulations of the Investigational Review Board of the institution. Patients had a CBC, chemistry profile, urinalysis, and clinical evaluation prior to each infusion, 24 hr and 7 days after infusion, and every 2 weeks until taken off the protocol. They also had a single measurement of serum total protein, albumin, IgA, IgG, and IgM immunoglobulin. A total immunoglobulin (total Ig) assessment was determined by summing IgA, IgG, and IgM values. All patients had serum creatinine and bilirubin levels within normal limits. Alkaline phosphatase, SGOT, and SGPT levels did not exceed three times normal. No patients had received more than one trial of chemotherapy (usually 5-fluorouracil with or without cisplatin). Each patient was assigned an arbitrary "tumor load" evaluation on a 1–5 scale based on the size, number, and multiplicity of organs involved in the metastatic process. This assessment was made by two independent investigators, who had no knowledge of the respective patients' pharmacokinetic data.

Study Design and Antibody Preparation

The patients were assigned randomly to one of two treatment groups and received either 10 mg ($n = 5$) or 40 mg ($n = 5$) as a single treatment. Six of the patients received either 10-mg ($n = 3$) or 40-mg ($n = 3$) every 14 days for a total of three doses. This study was designed to make optimal use of the limited supply of C-17-1A. The chimeric mouse/human monoclonal antibody was provided by Centocor (12) and purified from human tissue cultures as previously described (8,15). It was provided as a suspension of 1.5 mg/ml in 10-ml vials and contained <1% aggregates as determined by gel filtration high-pressure liquid chromatography (HPLC).

Drug Administration and Sample Collection

A 0.5-mg test dose was administered by intravenous bolus infusion. If no adverse reactions occurred within 30 min, the remainder of the dose was diluted in 200 ml of 0.9% sodium chloride for injection and administered as a constant rate infusion over 1 hr. Ten-milliliter blood samples were collected contralaterally before the administration of the test dose and at times 0, 1, 2, 4, 12, 24, 72, 168, 240, and 336 hr postinfusion for multiple-dose studies. Additional samples were collected in patients receiving a single dose. In some instances, samples were collected up to 1008 hr postinfusion. All samples were allowed to clot and were centrifuged. Serum was harvested, placed into appropriately labeled containers, and frozen at −20°C within 2 hr of collection.

Analytical Methods

C-17-1A concentration in serum was determined using the double-antibody technique of Midgely (16), which utilizes competitive inhibition of ^{125}I-C-17-1A and unlabeled C-17-1A binding to rabbit anti-M-17-1A $F(Ab)_2$ IgG antibody, as previously described (9). Standards were prepared in normal human serum to contain C-17-1A in concentrations of 1 to 500 μg/L. The intraassay coefficients of variation were <10% and interassay coefficients of variation were <15%.

Pharmacokinetic Analyses

Serum concentration versus time data for each patient, as well as the mean data, were evaluated using SIPHAR/base (SIMED, Creteil, Cedex, France). Initial parameter estimates were determined using a peeling algorithm (17) with and without correction for infusion time (18). Final parameter estimates were determined using a weighted least-squares nonlinear regression algorithm (19) with the weight set as the reciprocal of the calculated concentration. Both of these algorithms are a part of SIPHAR/base. Compartment model selection was made by visual inspection of the fit, evaluation of standard residual data, and comparison of the Akaike value. The following model-dependent pharmacokinetic parameters were calculated using previously described methods (20): distribution and elimination coefficients and rate constants (A, B, α, and β, respectively), distribution half-life ($t_{1/2_\alpha}$), elimination half-life ($t_{1/2_\beta}$), area under the curve to time infinity (AUC), total-body clearance (CL), steady-state volume of distribution (V_{ss}), volume of the central compartment (V_c), and the apparent volume of distribution (V_β). Theoretical steady-state maximum and minimum serum concentrations were predicted from mean single-dose parameter estimates and serum concentrations using biexponential linear pharmacokinetic models (21) and compared to the actual maximum and minimum concentrations observed on Day 14 and Day 28.

Statistical Evaluation

All group demographic and pharmacokinetic data are presented as mean ± SD. Comparisons between grouped data were made using a two-tailed Student's t test. Covariance determinations between demographic and pharmacokinetic parameters were conducted using linear least-squares regression analysis and included the following tests: correlation coefficient (r), the null hypothesis (H_o) that $r = 0$, and Student's t test, H_o, that the slope of the regression line was equal to zero. All statistical analyses used previously described methods (22,23). For all statistical evaluations, the level of significance accepted was $P < 0.05$.

RESULTS

Demographic and Laboratory Data

The demographic characteristics and selected mean laboratory data for the 10 patients enrolled in the study are

Table I. Demographic Data in Ten Patients with Adenocarcinoma of the Colon (Mean ± SD)

	10-mg group (n = 5)	40-mg group (n = 5)	p
Age (years)	47 ± 14	59 ± 12	NS
Gender (M:F)	1:4	5:0	—
Weight (kg)	70 ± 12	72 ± 17	NS
BSA (m^2)	1.8 ± 0.2	1.9 ± 0.2	NS
Albumin (g/dl)	3.5 ± 0.4	3.1 ± 0.6	NS
Total protein (g/dl)	7.0 ± 0.4	6.8 ± 0.5	NS
IgA (g/dl)	0.2 ± 0.1	0.4 ± 0.2	0.04785
IgG (g/dl)	1.1 ± 0.2	1.4 ± 0.8	NS
IgM (g/dl)	0.2 ± 0.1	0.2 ± 0.1	NS
Total Ig (g/dl)	1.5 ± 0.2	2.0 ± 1.0	NS
Tumor load	2.4 ± 1.8	3.2 ± 1.7	NS

presented in Table I. Six of the patients were male. Five of the male patients were enrolled in the 40-mg dose group, leaving one male and four females in the 10-mg group. No significant differences in laboratory values existed between the two groups with the exception of serum IgA.

Single-Dose Data

The mean serum concentration versus time data for both the 10-mg and the 40-mg single-dose groups are presented in Fig. 1. The disposition of both the 10-mg and the 40-mg doses of C-17-1A was best described by a two-compartment model. Table II provides the mean pharmacokinetic characteristics for both groups. The mean distribution half-lives for the 10-mg and 40-mg single-dose groups were 15.8 and 18.5 hr, respectively. The mean elimination half-lives for the 10-mg and 40-mg single-dose groups were 90.0 and 97.6 hr, respectively. The mean maximum and minimum serum concentrations for the 40-mg single-dose group (C_{max} = 13.32 ± 3.40 μg/ml and C_{min} = 0.59 ± 0.13 μg/ml, respectively) were approximately 3.5 times higher than those observed in the 10-mg single-dose group (C_{max} = 3.98 ± 1.01 μg/ml and C_{min} = 0.16 ± 0.13 μg/ml, respectively) reflecting the fourfold difference in dose. Similarly, the mean values for A and B were significantly different between the 10-mg and the 40-mg single-dose groups, with parameter values approximately 3.2 times greater in the 40-mg single-dose group. No significant differences were observed in C_{max}, C_{min}, A, B, or AUC between the 10-mg and the 40-mg single-dose groups when these parameters were normalized per milligram of C-17-1A administered. When expressed as micrograms per kilogram the doses administered to the 10-mg and 40-mg single-dose groups ranged from 130 to 880 μg/kg. A significant linear correlation existed between AUC expressed as (μg/ml) * hr and dose as μg/kg as shown in Fig. 2.

Table II. Comparison of C-17-1A Pharmacokinetics (Mean ± SD) Following Administration of 10 mg (n = 5) and 40 mg (n = 5) as a Single Dose Infused over One Hour

	10-mg group	40-mg group	p
C_{max} [(μg/L/mg)]	398 ± 101	333 ± 85	NS
C_{min} [(μg/L/mg)]	16 ± 13	15 ± 10	NS
A[(μg/L)/mg]	219 ± 72	173 ± 45	NS
α (1/hr)	0.044 ± 0.006	0.038 ± 0.007	NS
$t_{1/2\alpha}$ (hr)	15.8	18.5	—
B[(μg/L/mg)]	177 ± 70	142 ± 68	NS
β (1/hr)	0.008 ± 0.002	0.007 ± 0.002	NS
$t_{1/2\beta}$ (hr)	90.0	97.6	—
AUC [(μg/ml * hr)/mg]	29.8 ± 13.4	25.9 ± 9.1	NS
V_c (L)	2.65 ± 0.65	3.26 ± 0.58	NS
V_β (L)	4.85 ± 1.47	6.13 ± 2.64	NS
V_{ss} (L)	4.13 ± 0.97	5.16 ± 1.92	NS
V_{ss} (ml/kg)	59 ± 8	73 ± 19	NS
CL (ml/hr)	37 ± 14	40 ± 12	NS
CL (ml/hr/kg)	0.52 ± 0.16	0.61 ± 0.31	NS

No significant differences were observed in any of the mean volume or clearance values determined. The mean volume of distribution parameters not normalized for body weight were smaller in the 10-mg single-dose group than in the 40-mg single-dose group (V_c = 2.65 ± 0.65 and 3.26 ± 0.58 liters, respectively; V_{ss} = 4.13 ± .97 and 5.16 ± 1.92 liters, respectively; and V_β = 4.85 ± 1.47 and 6.13 ± 2.64 liters, respectively). Normalization for body weight did not alter this finding (V_{ss} = 59 ± 8 and 73 ± 19 ml/kg for the 10-mg and 40-mg single-dose groups, respectively). Total-body clearance for both groups varied considerably between patients (19 to 55 and 24 to 52 ml/hr for the 10-mg and 40-mg groups, respectively). The mean total-body clearance was higher in the 40-mg group (CL = 37 ± 14 and 40 ± 12 ml/hr and 0.52 ± 0.16 and 0.61 ± 0.31 ml/hr/kg for the 10-mg and 40-mg groups, respectively) but these differences were not significant.

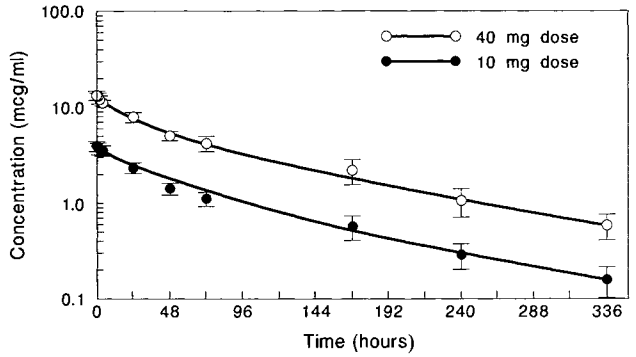

Fig. 1. Mean serum concentration versus time data for C-17-1A 10-mg (n = 5) and 40-mg (n = 5) single-dose groups. Filled symbols represent 10-mg data and open symbols represent 40-mg data.

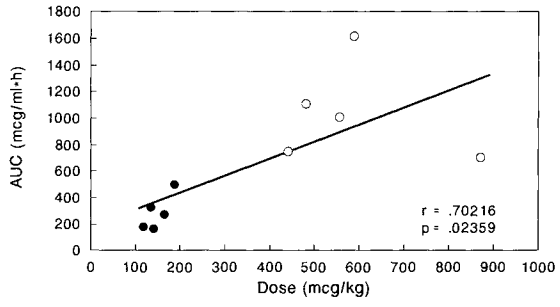

Fig. 2. Relationship between C-17-1A area under the curve and dose. Filled symbols represent 10-mg data and open symbols represent 40-mg data. AUC = 1.25 * dose + 204.

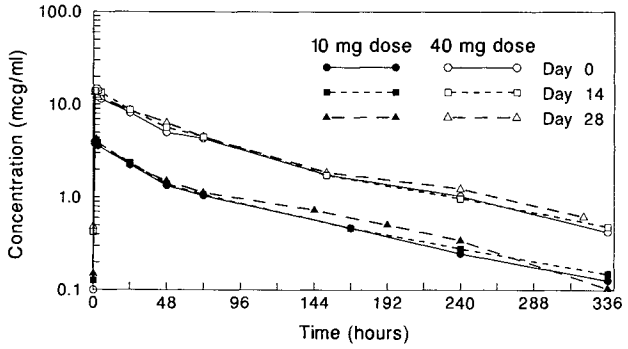

Fig. 3. Mean serum concentration versus time data for C-17-1A 10-mg (n = 3) and 40-mg (n = 3) multiple-dose groups. Filled symbols represent 10-mg data (●, Day 0; ■, Day 14; ▲, Day 28) and open symbols represent 40-mg data (○, Day 0; □, Day 14; △, Day 28).

Multiple-Dose Data

The mean serum concentration versus time data in six patients (four men and two women) receiving either the 10-mg or the 40-mg dose every 14 days is presented in Fig. 3 and Table III. At both doses the mean serum concentrations on Day 14 and Day 28 were virtually superimposable with the Day 0 data. This was also observed within each individual patient (data not shown). No significant differences were observed within a given dose group in C_{max}, C_{min}, or AUC from the first through the third infusion. As anticipated and observed in the single-dose analyses, the C_{max} and C_{min} values for the 40-mg group were approximately four times higher (range, 3.2 to 4.8) than those for the 10-mg group. Similarly, the mean AUC values for the 40-mg group were 3.5 times higher than the 10-mg group, reflecting the fourfold difference in dose. Examination of the pharmacokinetic characteristics for each patient receiving multiple infusions of C-17-1A demonstrated consistent values for all three administrations (data not shown).

Pharmacokinetic and Demographic Correlations

To examine the factors influencing the pharmacokinetics of C-17-1A following single-dose administration, linear regression analyses were conducted between demographic/laboratory values and pharmacokinetic parameters. A summary of these correlations is provided in Table IV. No significant relationships were observed between the demographic and the laboratory values tested and any of the C-17-1A distribution volumes. In contrast, significant correlations were observed between C-17-1A total-body clearance and circulating total Ig levels and between C-17-1A total-body clearance and circulating IgG levels (Fig. 4). No correlation was observed between C-17-1A total-body clearance and either IgA or IgM. In addition, significant correlations were observed between C-17-1A total-body clearance and tumor load (Fig. 5), total Ig and tumor load, and IgG and tumor load. No correlation was observed between either IgA or IgM and tumor load.

DISCUSSION

A summary of the general pharmacokinetics of C-17-1A has been presented in a previous publication (9). The mean distribution volumes of C-17-1A (mean V_c = 2.7 and 3.3 liters and V_{ss} = 4.1 and 5.2 liters for the 10-mg and 40-mg single-dose groups, respectively) indicate that C-17-1A appears to distribute throughout the vascular compartment and limited extravascular space. These findings were consistent with physiologic data and the reported distribution volumes for M-17-1A (2.7 to 4.0 liters/70 kg) (13), native IgG (3.7 ± 0.7 liters/70 kg) (24), and other murine monoclonal antibodies (25,26). The total-body clearance of C-17-1A (0.52 and 0.61 ml/hr/kg for the 10- and 40-mg single-dose groups, respectively) was approximately 25% of the clearance reported for M-17-1A (1.9 to 2.6 ml/hr/kg) (13). The disposition of C-17-1A resulted in a biexponential decline in plasma concentration, with a mean elimination half-life ($t_{1/2_\beta}$ = 90.0 and 97.6 hr for the 10-mg and 40-mg single-dose groups, respectively) that was intermediate between M-17-1A (mean $t_{1/2}$ = 14.4 to 25.3 hr) (13) and IgG (mean $t_{1/2}$ = 21 days) (24).

A fourfold increase in C-17-1A dose produced approximately 3.5-fold increases in mean C_{max}, C_{min}, and AUC, with no significant differences in mean pharmacokinetic parameters (V_c, V_{ss}, V_β, CL, $t_{1/2_\alpha}$, and $t_{1/2_\beta}$) in the dosage range studied (10 to 40 mg or 130 to 880 μg/kg). Accordingly, a linear correlation was observed between AUC as μg/ml * hr and dose as μg/kg (see Fig. 2). Our data indicate that C-17-1A exhibited nonsaturable distribution and elimination characteristics in the dosage range studied. These findings were in contrast to those of Rosenblum *et al.* (27), who reported a reduction in the apparent volume of distribution of anti-p97 murine monoclonal antibody from 7.8 ± 0.7 liters at a 1-mg dose to 3.0 ± 0.1 liters at a 20-mg dose, suggesting saturation of antigenic or other extravascular binding sites at higher doses. However, their data also indicated a reduction in AUC/mg dose administered as the dose was increased. Our findings were also in contrast to those of Koizumi *et al.* (28), who reported that the clearance of ^{123}I-Lym-1 monoclonal antibody in patients with B-cell lymphoma was pro-

Table III. Comparison of Grouped C-17-1A Serum Concentration (Mean ± SD) Data Following Administration of 10 mg (n = 3) or 40 mg (n = 3) in Multiple Doses Infused Over One Hour on Days 0, 14, and 28

	Day 0	Day 14	Day 28
C_{max} 10 (μg/ml)	3.96 ± 6.67	3.83 ± 0.81	3.92 ± 0.45
C_{min} 10 (μg/ml)	0.13 ± 91	0.15 ± 0.11	0.13 ± 0.09
AUC 10 (μg/ml * hr)	268 ± 74	284 ± 114	291 ± 117
C_{max} 40 (μg/ml)	13.29 ± 3.56	13.43 ± 1.36	13.00 ± 3.17
C_{min} 40 (μg/ml)	0.42 ± 0.32	0.48 ± 0.26	0.61 ± 0.32
AUC 40 (μg/ml * hr)	939 ± 210	989 ± 140	1028 ± 198

Table IV. Pharmacokinetic and Demographic Comparisons

Comparison	*r*	*p*
CL vs total Ig	0.69102	0.02998
CL vs IgA	0.40946	NS
CL vs IgG	0.70846	0.02184
CL vs IgM	0.59781	NS
CL vs tumor load	0.71813	0.01933
Total Ig vs tumor load	0.76203	0.01041
IgA vs tumor load	0.59638	NS
IgG vs tumor load	0.76932	0.00928
IgM vs tumor load	0.34412	NS

foundly decreased as the amount of antibody injected was increased, indicating apparent saturation of the antibody's elimination.

The mean pharmacokinetic characteristics of C-17-1A following multiple administration were remarkably similar to the mean single dose values. The mean C_{max} and C_{min} observed on Day 14 and Day 28 for both the 10-mg and the 40-mg were in good agreement with the theoretical values predicted using an accumulation factor of 1.073 determined from the mean elimination rate constant of both the 10 and 40 mg dose groups on Day 0. The significance of this reproducibility has been discussed (9). It provided pharmacokinetic evidence suggesting that C-17-1A did not produce a substantive antibody response which would have increased the clearance of the compound. These findings were in agreement with the immunologic data for C-17-1A, which indicated that only one of 10 patients developed an antiantibody response when assayed by a "double-antigen" system (9). This distinguishes C-17-1A from native antibodies, which have been reported to cause pronounced anti-monoclonal antibody responses and to be rapidly cleared upon multiple-dose administration (2,4,29,30).

The correlation observed in our patients between C-17-1A total-body clearance and circulating total Ig levels appears to be attributable to the relationship between C-17-1A total body clearance and circulating IgG levels (Fig. 4), since no correlations were observed between C-17-1A total-body clearance and either circulating IgA or IgM. Our data are in agreement with the observations of Morell *et al.* (24), who reported that elevated serum concentrations of any IgG subclasses in patients with multiple myeloma were associated with a shortened biologic half-life and an increased catabolic rate of all subclasses. These observations are also consistent with the findings of Solomon *et al.* (31), who reported that the rate of γ-globulin catabolism was increased in patients with multiple myeloma who had elevated total serum proteins.

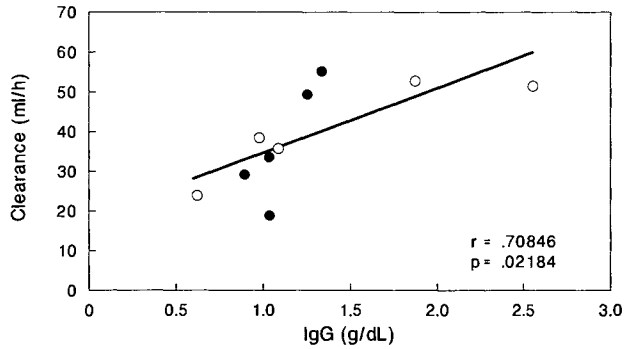

Fig. 4. Relationship between C-17-1A total-body clearance and circulating IgG levels. Filled symbols represent 10-mg data and open symbols represent 40-mg data.

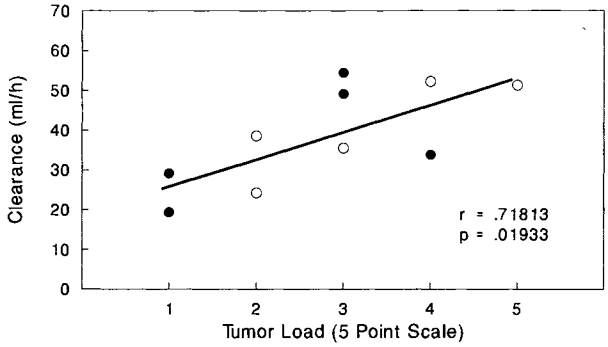

Fig. 5. Relationship between C-17-1A total-body clearance and tumor size. Filled symbols represent 10-mg data and open symbols represent 40-mg data. Relative tumor size was based on physical assessment and laboratory data, where 1 is the smallest category and 5 is the largest category.

The linear correlation observed in our patients between C-17-1A total-body clearance and tumor size (Fig. 5) is a most interesting finding. This trend appears to be present in both the 10-mg and the 40-mg single-dose data. To our knowledge no previous reports exist regarding a relationship between tumor size or tumor load and antibody clearance. Clearly, a direct relationship of this nature is reasonable if binding of antibody to tumor cells results in the removal of C-17-1A from plasma and antibody catabolism. Therefore, the greater the tumor load, the greater the binding of available C-17-1A and the higher the clearance of compound. Another explanation may be that accelerated catabolism of proteins is associated with the elevation of total serum proteins that occurs with increasing tumor burden (24,31). This indirect relationship between tumor load and C-17-1A clearance is supported by the correlations observed in our patients between total IgG and tumor load and between IgG and tumor load. Further data with larger numbers of patients will be needed to confirm this observation in our pilot study.

In conclusion, the administration of 10-mg and 40-mg infusions of C-17-1A to 10 patients with metastatic adenocarcinoma resulted in distribution volumes that were in accord with physiologic data; in nonsaturable, linear elimination characteristics, with clearance and half-life values that were intermediate between M-17-1A and native human IgG; in nearly identical single-dose and multiple-dose pharmacokinetic characteristics, with predictable multiple-dose plasma concentrations; and in significant correlations between C-17-1A clearance and total Ig, IgG, and tumor load. Our AUC versus dose observations are limited to the 10- to 40-mg (130- to 880-μg/kg) doses used in our investigations. The administration of doses up to 400 mg is under consideration and will provide additional insights into this relationship. Further studies with multiple-dose administration of C-17-1A are needed to provide additional information re-

garding the immunogenicity and catabolism of chimeric monoclonal antibodies in man.

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