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ORIGINAL ARTICLE

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Survival benefit associated with human anti-mouse antibody (HAMA) in patients with B-cell malignancies

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Abstract *Background*: About one-third of patients with relapsed B-cell malignancies develop human anti-mouse antibody (HAMA) following mouse antibody treatment. The purpose of this study was to assess the relationship between HAMA and survival in patients given a mouse anti-lymphoma monoclonal antibody (mAb), Lym-1, directed against a unique epitope of HLA-DR antigen that is up-regulated on malignant B-cells. *Methods*: ELISA was used to quantify HAMA in 51 patients with B-cell malignancies treated with iodine-131 (^{131}I) labeled Lym-1. Sera were collected prior to and following radioimmunotherapy (RIT) with ^{131}I-Lym-1 until documented to be HAMA negative or throughout lifetime. Univariate, then multivariate analyses including other risk factors, were used to analyze the relationship of HAMA to survival. The relationships of HAMA to prior chemotherapies and to absolute lymphocyte counts prior to RIT were also assessed. *Results*: Eighteen of 51 patients (35%) developed HAMA following RIT (range of ultimate maximum titers, 6.6–1,802 μg/ml). Using the time dependent Cox proportional hazards model, maximum HAMA titers were associated with survival ($P = 0.02$). HAMA continued to be significant for survival in multivariate analyses that included known risk factors. In Landmark analysis of 39 patients that survived at least 16 weeks, median survival of patients with HAMA less than 5 μg/ml was 61 versus 103 weeks for patients with HAMA equal or greater than 5 μg/ml at 16 weeks ($P = 0.02$). The median survival of the five patients with highest maximum HAMA titers was 244 weeks. At 16 weeks, there was an inverse correlation between the maximum HAMA titer and the number of previous chemotherapies ($P < 0.003$). Absolute lymphocyte counts prior to ^{131}I-Lym-1 treatment for patients that seroconverted were higher than those for patients that did not seroconvert ($P = 0.01$). *Conclusions*: Patients with B-cell malignancies that developed high HAMA titers had longer survival that was not explained by risk factors or histologic grade, suggesting the importance of the immune system.

Keywords Non-Hodgkin's lymphoma · Radioimmunotherapy · Survival · Human anti-mouse antibody · Monoclonal antibody · HLA-DR

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Introduction

Immunotherapy and radioimmunotherapy (RIT) using mAbs have favorable efficacy–toxicity profiles in B-cell malignancies, such as non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL) [1–5]. A polyclonal human antibody response, either anti-isotypic or anti-idiotypic in nature, can occur whether the administered mAb is mouse or has been "humanized", albeit the frequency and titer are higher in the former circumstance [6]. Although the clinical sequelae of human anti-mouse antibody (HAMA) are usually minor [7–9], subsequent treatment may be affected by rapid clearance of the mAb from the blood [10]. Seroconversion frequencies range from 1 to 35% in patients with relapsed B-cell malignancies and from 40 to 100% in patients with solid tumors [1, 11–15], in part reflecting

known differences in the immunocompetence of these patients.

A survival benefit, linked to the development of anti-idiotypic antibodies, has been reported for HAMA [13, 16–18]. The purpose of this study was to assess the relationship between HAMA and survival in patients with B-cell malignancies given multiple doses of a mouse anti-lymphoma mAb, Lym-1, directed against an HLA-DR antigen up-regulated on malignant B-cells [19]. HLA-DR binds exogenously-derived peptides providing a repertoire of peptides on the surface of antigen-presenting cells for inspection by CD4 positive T cells. HLA-DR residues critical for Lym-1 binding are in the immediate area of the peptide presenting pit. HAMA was mentioned briefly in an earlier examination of 27 radiolabeled Lym-1 treatment factors [20]. Because of the potential importance of an association of HAMA and survival to the future clinical management of patients with B-cell malignancies, the data herein represent an in depth survival analysis and discussion. Additionally, biostatistical evaluations to assess whether the association between HAMA and survival could be explained by known risk factors for these malignancies or factors known to be related to immune competence have been conducted.

Methods

Patient selection

Fifty-three heavily pretreated patients with relapsed B-cell malignancies, who were progressing despite standard therapy, were entered in either of two consecutive phase I/II trials designed to determine the safety and preliminary efficacy of multiple doses of ^{131}I-Lym-1 [1, 2]. A dose of unconjugated Lym-1 was infused immediately before each ^{131}I-Lym-1 treatment (or imaging study), Lym-1 reactivity with their malignant lymphocytes, measurable disease, adequate bone marrow and blood count status, and a negative baseline HAMA titer were documented in all of the patients. Although the individual ^{131}I-Lym-1 treatment doses (mCi) were larger in the second trial, the final patient populations (see next paragraph) were remarkably similar with respect to age, Karnofsky performance status (KPS), histologic grade, Ann Arbor stage, prior therapies, International prognostic index (IPI), serum lactic dehydrogenase, and overall response rate from I-131 Lym-1 treatment (Table 1). HAMA frequencies and titers were also similar in the two patient populations. Before therapy all patients were advised of the investigational nature of the study, and signed an informed consent for protocols that were approved by the University of California at Davis Human Subjects and Radiation Use Committees under an Investigational New Drug authorization from the United States Food and Drug Administration.

Of the 53 patients entered in the trials, 51 were evaluable for HAMA response. Two patients were excluded because of death on days 2 and 9 after initial exposure to Lym-1; in these two patients there was insufficient time to develop HAMA [3]. The patient population included 31 males and 20 females. Median KPS was 70 (range 40–90), and median age was 54 years (range 29–74). Histologic grade included 8 patients with high-grade, 27 intermediate-grade and 16 low-grade NHL. Five patients with CLL and adenopathy are included in the latter group. Forty-seven patients were Ann Arbor stage IV NHL and four were stage III.

Table 1 Similarity of the characteristics of the patients entered in the two trials

Characteristic	Trial no. 1	Trial no. 2
No. of patients	29	22
Mean age (range)	54 (29–74)	57 (33–71)
Multiple dose trial design	Yes	Yes
Mean IPI	3.3	3.3
Mean KPS (range)	67 (40–90)	72 (60–90)
Ann Arbor stage 4/3	26/3	21/1
Grade: low/intermediate/high	34/45/21%	23/64/13%
Elevated LDH	19 (66%)	10 (45%)
Mean prior therapies (range)	4 (1–13)	4 (1–9)
Overall response rate	57%	52%
HAMA frequency	10 (34%)	8 (36%)
Mean total Lym-1 mg (range)	191 (8–887)	147 (52–320)

Study design

Human anti-mouse antibody was titered before, during and after RIT until death [21]. Because these trials were designed for administration of multiple doses of ^{131}I-Lym-1, they provided an opportunity to characterize HAMA and survival over time. The date of first treatment with ^{131}I-Lym-1 was uniformly used for all time dependent analyses HAMA seroconverters fell into either of two categories differing in seroconversion time and titer. HAMA titer was considered in the analyses in addition to simple seroconversion status. Possible relationships between maximum HAMA titer, survival and known risk factors were assessed. In an earlier multivariate analysis of factors prognostic for RIT outcomes in B-cell malignancies, pretherapy serum LDH and KPS best predicted survival, complete and partial remission and time to progression after ^{131}I-Lym-1 treatment [22]. A risk factor index based on LDH and KPS, and the IPI (that includes these and three other factors and has been reported to be predictive of chemotherapy outcomes [23]) were used to test the significance of HAMA titer in time dependent, multivariate proportional hazards analyses of survival. The relationships of HAMA to prior chemotherapies and to absolute lymphocyte counts prior to RIT were also assessed.

Pharmaceuticals

Lym-1 (Damon Biotechnology, Needham Heights, MA, USA or Techniclone, Inc., Tustin, CA, USA) is an

IgG2a mouse mAb with high affinity against a discontinuous epitope of the beta chain of the HLA-DR10 antigen up-regulated on the surface membrane of malignant B-lymphocytes [19]. The Lym-1 antigen is not modulated, and Lym-1 activates antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and direct cytotoxicity on target Raji human NHL cells in vitro [24, 25].

Lym-1 was labeled with ^{131}I using chloramine-T at a mass ratio of 1–10 μg of Lym-1, and high specific activity ^{131}I sodium iodide in 0.05N sodium hydroxide. Radioiodination provided radiolabeling efficiencies of 97 ± 2% and ^{131}I-Lym-1 specific activities of 10 mCi/mg of Lym-1.

HAMA assay

Serum samples were obtained from each patient prior to exposure to ^{131}I-Lym-1 (baseline), prior to each subsequent ^{131}I-Lym-1 treatment, 1 month and biannually after the last ^{131}I-Lym-1 treatment. HAMA titers were quantified using a two-step detection method in an ELISA format and 96-well plates (PRO-BIND™' Becton Dickinson, Lincoln Park, NJ, USA), as described [21]. Briefly, Lym-1 coated plates with non-specific binding sites blocked were used to capture HAMA. The captured IgG was detected and amplified in a second step using biotinylated goat anti-human IgG (Amersham, Arlington Heights, IL, USA) or biotinylated mouse anti-human IgG (Sigma, St. Louis, MO, USA) followed by streptavidin-horseradish peroxidase (Amersham) and ABTS substrate (Sigma). The optical density of each well was read at 405 nm in an ELISA reader (Dynatech MR-300, Chantilly, VA, USA). Serial twofold dilutions of serum containing a known amount of HAMA were used to generate a reference standard curve for each ELISA assay to quantify each patient's HAMA titer. The HAMA titer was defined as the amount in the patient's least-dilute sample that fell within the linear portion of the standard curve. For treatment purposes a positive HAMA was defined as a value greater than 5 μg/ml. This value was selected because it was four standard deviations above the mean of the baseline titer for a group of 15 volunteers. The maximum HAMA titer was defined as the highest HAMA titer observed for a patient among all follow-up samples, and may not have represented the true maximum in the patients that died. For time dependent analyses, the maximum HAMA titer up to that point in time was used.

Statistical analysis

Statistical analyses were carried out using SAS version 6.08 or greater and Statview 4.1 for Macintosh [26]. To evaluate the effect of HAMA on survival, two different analyses were used: (1) the Cox proportional hazards model; and, (2) the Landmark method. In the proportional hazards model, the maximum HAMA titer was defined as a time dependent variable. At each point in time, the maximum HAMA observed for the patient up to that point in time was included to assess risk. When data include extreme values, the relationship can often be more accurately described assuming a linear relationship with a log transformation of the predictor values. For this analysis the natural logarithm of the HAMA titers was used to minimize the effects of the few very high HAMA values. All patients were assigned a score of zero at baseline (based on the fact that all were considered HAMA negative at the start of the study). For patients that seroconverted, the HAMA score in the model was reset at the time of each HAMA evaluation and the natural log of the maximum HAMA titer to that time was used. As an alternative method to eliminate potential for bias, the Landmark method [27] was used including only those patients with a survival over 16 weeks and defining the maximum HAMA titer for each patient to be the maximum up to this point in time. This period of time was selected because at 16 weeks, 15 patients (83%) of the 18 ultimately positive had developed a HAMA and only 12 patients had died (Table 2). Eleven of 18 seroconverters had reached their ultimate maximum HAMA titer by 16 weeks. The survivals of seroconverting patients at that time were compared with those of patients that were HAMA negative, or had a low HAMA titer, using the log rank test. Analysis of HAMA titer as a predictor was also repeated using the proportional hazards model and the maximum HAMA titer to 16 weeks. Since HAMA did not change over time for this analysis, a time dependent model was not required. The Landmark analysis evaluated HAMA for all surviving patients at a fixed point following the onset of treatment and avoided the bias of including patients who died early in the HAMA negative group. To further evaluate the role of HAMA as a predictive factor, the proportional hazards model was repeated adjusting for risk factors by including either the widely used IPI [23] or a risk score based on our experience using LDH and KPS for RIT outcomes [22]. Finally, to assure that the conclusions did not depend on histologic grade, the time dependent proportional hazards model was fit for the patients with low and intermediate grade histologies

Table 2 Number of initial 51 patients seroconverting and surviving at each time point following first ^{131}I-Lym-1 treatment

Time (weeks)	Seroconverters	Survivors
4	7	48
12	14	40
16	15	39
20	17	35
24	17	30
43	18	26

All HAMA seroconverters (18 patients) had done so by 43 weeks. Sixteen weeks was chosen for the Landmark model as an appropriate compromise between the number of seropositives and survivors

separately. Since the results from these subset analyses were similar to the overall results, only the overall results are presented.

Survival curves were estimated based on the method of Kaplan–Meier [28]. Survival was measured from the date of first treatment with ^{131}I-Lym-1, to death or to the date of this analysis; one patient was alive at this time. The relationship of HAMA seroconversion at 16 weeks and absolute lymphocyte count prior to ^{131}I-Lym-1 treatment was assessed using the Wilcoxon rank sum test; seven patients with large numbers of circulating malignant lymphocytes were not included in this analysis. The association of maximum HAMA by 16 weeks with the number of prior chemotherapies [7] was analyzed using the Spearman rank correlation coefficient.

Results

Eighteen (35%) of 51 patients developed a positive HAMA (seroconverted) after exposure to Lym-1. The frequency of seroconversion was not related to protocol, histologic grade, or risk factors (Table 3). For those patients that seroconverted, the median for their ultimate maximum HAMA titer was 87.6 (range 6.6–1,802) μg/ml, and the median time after first ^{131}I-Lym-1 treatment to reach the observed maximum titer was 10 (range 3.4–47.4) weeks. Of 18 patients that seroconverted, 13 did so early (median 4.4 weeks) and after 1–3 exposures, whereas 5 patients did so later (median 16 weeks) and after 4–7 exposures to ^{131}I-Lym-1. Maximum HAMA titers were higher in the early seroconverters, even though they had received fewer doses/exposures and equivalent amounts of Lym-1 than the late seroconverters. The former group had a median for their ultimate maximum HAMA titer of 148.2 (range 9.9–1,802) μg/ml where as the 5 late seroconverting patients had a median for maximum titer of 10.3 (range 6.6–118) μg/ml.

Table 3 Relationship of seroconversion to protocol, histologic grade and risk factors

	HAMA negative	HAMA positive	*P* value[a]
Protocol			
1	19 (58%)	10 (56%)	0.81
2	14 (42%)	8 (44%)	
Grade			
Low	8 (24%)	7 (39%)	0.40
Intermediate	19 (58%)	8 (44%)	
High	6 (18%)	3 (17%)	
IPI			
1	4 (12%)	0 (0%)	0.62
2	3 (9%)	5 (28%)	
3	10 (30%)	5 (28%)	
4	11 (33%)	6 (33%)	
5	5 (15%)	2 (11%)	
Risk level (LDH, KPS)			
0	9 (27%)	8 (44%)	0.39
1	14 (42%)	5 (28%)	
2	10 (30%)	5 (28%)	

[a]Based on Cochran Mantel Haenszel test for ordered catergories

From time of first ^{131}I-Lym-1 treatment, the median survival of the 51 patients was 45 weeks. The median survival of the 5 patients with highest maximum HAMA titers (all greater than 1,000 μg/ml) was 244 (range 61–579) weeks.

There was an association between maximum HAMA titer and survival in the time dependent Cox proportional hazards model ($P = 0.02$). HAMA titer remained a statistically significant factor ($P < 0.05$), even when adjusted for risk categories based on LDH and KPS 13), or IPI [23]. Using all 51 patients, the univariate proportional hazards model showed that for every $\log_e$ unit increase in HAMA, the risk of dying was decreased by a factor of 0.86 (hazard ratio), as a time dependent variable ($P = 0.02$, c.i. = 0.76–0.98). The data were also analyzed using the Landmark model (Fig. 1). This method of analysis evaluated HAMA for all surviving patients at 16 weeks following initial ^{131}I-Lym-1 treatment thereby avoiding potential bias of including patients who died early in the HAMA negative group. Sixteen weeks was selected as the Landmark time point because 15 of 18 seroconverters had a positive HAMA by that time and only 12 patients had died (Table 2). Repeating the proportional hazards model using the maximum HAMA achieved by 16 weeks (so that a time dependent model was not required) provided similar results. The hazard ratio was 0.84 with $P = 0.02$. Given that HAMA thresholds for patient survival have been described by others [13], we evaluated three thresholds for HAMA titer using Landmark analyses. The median survival for the 27 HAMA negative patients was 61 weeks, whereas it was 103 weeks for the 15 patients with positive HAMA titers by 16 weeks ($P = 0.02$). Similar results were seen when thresholds of 20 and 80 μg/ml were used. The actuarial survivals at 2 years were 26, 27 and 28% versus 50, 56 and 57%, for the patients with values below and above the thresholds of 5, 20, and 80 μg/ml, respectively ($P \leq 0.02$) (Table 4). Considering those patients alive at 16 weeks, there was an inverse correlation between the maximum HAMA titer to that time and the number of previous chemotherapy regimens, using the Spearman rank correlation ($P < 0.003$) (Fig. 2). Furthermore, absolute lymphocyte counts prior to ^{131}I-Lym-1 treatment for patients that seroconverted were higher than those for patients that did not seroconvert ($P = 0.01$).

Discussion

Patients with B-cell malignancies have been documented to be immunodeficient [29]. This is the first detailed report showing a survival benefit for a group of patients that seroconverted following mAb treatment for B-cell malignancies. Using the time dependent Cox proportional hazards method and the maximum HAMA titer

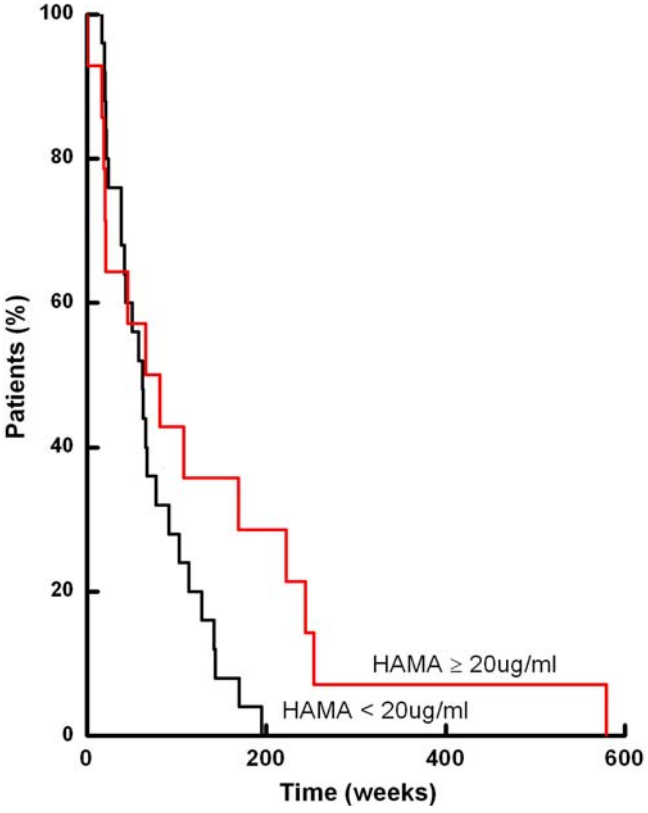

Fig. 1 Kaplan–Meier survival curves for 39 patients who survived at least 16 weeks from initial ^{131}I-Lym-1 treatment and categorized according to HAMA titer (μg/ml) by 16 weeks. Comparison of the two patient populations by the log-rank test demonstrated a significant survival advantage for patients whose HAMA titers were positive (Table 4). Survival time for the one patient in the HAMA positive group surviving to the date of the analysis (932 weeks) is not shown on the graph

Table 4 Association of maximum HAMA titer at 16 weeks (5, 20, or 80 μg/ml) with survival using the Landmark model on 39 patients alive at 16 weeks

n	Maximum HAMA (μg/ml)	*P* Value[a]	Survival at 2 years (%)[b]
27	< 5	0.02	26
12	≥5		50
30	< 20	0.02	27
9	≥20		56
32	< 80	0.01	28
7	≥80		57

[a] *P* values were obtained using the log-rank method and represent an overall assessment of the difference in survival between the two groups of patients

[b] Estimates of survival at 2 years derived from the Kaplan–Meier curves

up to each point in time for all 51 patients, HAMA was significantly and directly related to patient survival. In order to further assure that there was no bias in the assessment, the Landmark method of analysis was also used at 16 weeks after initial ^{131}I-Lym-1 treatment. This time point was chosen because 39 of 51 patients

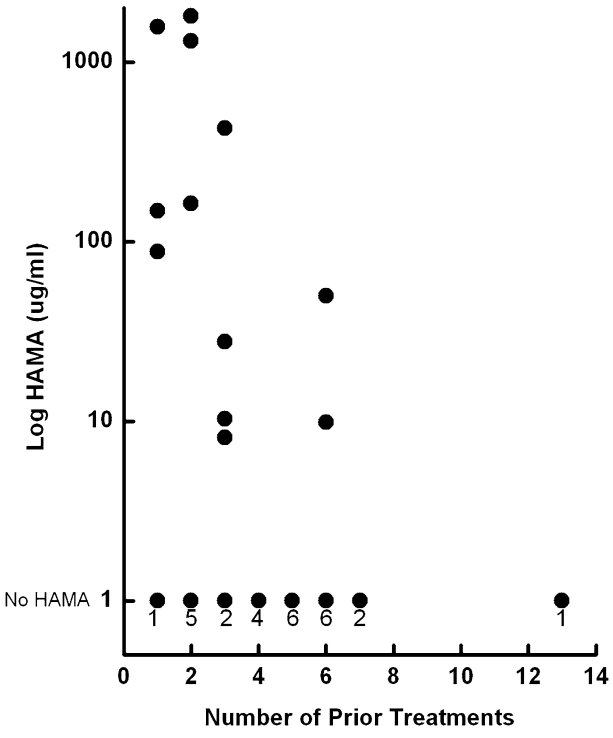

Fig. 2 A graphic depiction of the negative Spearman correlation between the log of maximum HAMA titers and the number of prior chemotherapies for the 39 patients who were alive at 16 weeks. All patients that failed to develop HAMA were assigned the value of 0. As there were several HAMA negative patients with the same number of prior treatments, the number of seronegative patients with the number of prior treatments is given below each *symbol* with a value of 0. The Spearman correlate, *rho*, was −0.47 with $P < 0.003$

remained alive and 15 of the 18 seroconverting patients had done so, 11 of these having reached their ultimate maximum by that time. For patients still alive at 16 weeks, the presence of HAMA remained significantly related to survival. For patients with positive HAMA at 16 weeks, the estimated 2-year survival was twice that for the patients failing to seroconvert. If the analysis threshold for HAMA titer was increased, survival advantage was retained. HAMA seroconversion and titer were not related to the number of doses/exposures and amounts of Lym-1 received by these patients [21]. Additionally, no relationship between HAMA and risk categories for these malignancies was observed; HAMA remained significantly related to survival in multivariate analyses that considered known risk factors.

"Humanized" antibodies have been engineered for use in immunotherapy and radioimmunotherapy. One of the most successful of this class of therapeutics, rituximab (Rituxan®) has achieved widespread use in the treatment of NHL because of its attractive efficacy and adverse event profiles [4]. B-cell depletion occurs because this chimerized anti-CD20 mAb has potent cytocidal effects on both normal and malignant B-lymphocytes. Highly durable remissions have been reported for subsets of patients treated with two other anti-CD20 mAbs, ^{131}I-tositumomab (Bexxar™) and ^{90}Y-ibritumomab

tiuxetan (Zevalin™) [30–32]. Currently, intense study is underway to define the nature and extent of these extended remissions. However, they are likely unrelated to HAMA for the following reasons. With either of these drugs as a pretreatment, a large amount of unconjugated mAb, that induces B-cell depletion, is given. Induction of HAMA is rare (less than 1%) following ^{90}Y-ibritumomab tiuxetan with rituximab pretreatment [31]. HAMA occurs more frequently with tositumomab (up to 8% in patients having previously received chemotherapy) likely because both pretreatment and treatment mAbs are mouse in origin [3]. When used as first line therapy for follicular lymphoma, tositumomab had a higher HAMA rate [33]. There may be another relevant difference between the anti-CD20 mAbs and Lym-1. Lym-1 binds to a unique epitope that includes the same HLA-DR beta chain residue, R71, that binds antigenic peptides displayed on HLA-DR [19]. Furthermore, Lym-1 does not reduce the peripheral blood lymphocyte count but does decrease the number of circulating malignant lymphocytes [25].

It has been reported that cancer patients developing a HAMA after mAb exposure can have unexpectedly prolonged survival [11, 13, 34–37], but the relationship between HAMA and survival is controversial [11, 13, 18, 35, 37, 38]. To date, the largest trial using unconjugated mAb for randomized adjuvant therapy in colon cancer failed to show a clear survival benefit related to HAMA [39], although an earlier, randomized trial by the same group did show that the mouse mAb "extend(ed) life and prolong(ed) remission" [14]. These discrepancies may be explained by failure of the analyses to consider the requirement for a threshold HAMA titer [13]. Miotti et al. [13] showed that 88% of the patients treated with a bispecific antibody for ovarian cancer had a HAMA but only patients with HAMA titers greater than 150 μg/ml (56% of the HAMA positive patients) showed a survival advantage. Similarly, higher HAMA titers were associated with longer survivals in our patients treated with ^{131}I-Lym-1. Evidence supporting the hypothesis that the survival benefit incident to HAMA is related to an idiotypic antibody cascade that includes the development of anti-idiotypic antibodies (Ab2) and anti-anti-idiotypic antibodies (Ab3), reflecting mirror images of the cancer antigen and the administered mAb, respectively, has been described [16, 17, 40, 41]. In one of our patients, direct evidence for initiation of a multilevel idiotypic cascade that was associated with prolonged disease-free survival was documented [42]. This patient with aggressive, Ann Arbor stage IV NHL developed within 1 month of initial ^{131}I-Lym-1 treatment a high HAMA titer that was sustained over her 9-year survival. The HAMA reflected an idiotypic cascade that consisted mostly of anti-idiotypic antibodies that included anti-Lym-1 specific antibodies (Ab2) and antibodies (Ab3) potent in a cytotoxicity assay (ADCC) against Raji human Burkitt's NHL cells [16, 42]. The patient's prolonged survival despite aggressive, advanced stage NHL may, thus, be understood in the context of the generation induced by ^{131}I-Lym-1 treatment of HAMA and endogenous, self-perpetuating tumor-specific antibodies.

Although these observations remain to be confirmed and their exact implications for immunotherapy and radioimmunotherapy, and mAb choices therein, remain to be determined, their clinical significance for the management of cancer, specifically NHL, seems important because the observations underscore the need to consider the immune implications of treatment. Certainly, the choice of mAb seems relevant despite appreciation that complex factors are involved. Specific to the Lym-1 mAb, it binds poorly to normal lymphocytes and its HLA-DR epitope is up-regulated on malignant lymphocytes [19]. HLA-DR is the most highly represented HLA class II subset. Furthermore, Lym-1 binds the same HLA-DR beta chain residue that binds exogenously-derived antigenic peptides displayed on HLA-DR [19]. These factors are worthy of consideration in view of the presumed generation of an idiotypic antibody cascade in an immune deficient population of patients.

Among the patients alive at 16 weeks, there was an inverse relationship between the maximum HAMA titer to that time and the number of previous chemotherapies. This observation is not surprising given the effect of the aforementioned therapies on the responsiveness of the human immune system. Further evidence in support of an immune basis for the survival advantage associated with seroconversion was provided by the significantly higher absolute number of lymphocytes prior to ^{131}I-Lym-1 treatment in patients that seroconverted.

The pivotal role of B and T cells in immune surveillance, and the depleting effect of cytotoxic therapies on these cells, has been recognized, documented and expanded upon for several decades. One scenario for a revised cancer treatment strategy is that proposed by Timmerman [43] who suggested that immunosuppressive drugs be deferred until later (unless curative). This would allow for initial activation of the antibody repertoire before treatment-induced abrogation of the host's ability to mount an immune response.

In summary, elevated HAMA titer was associated with survival benefit in patients with B-cell malignancies, putatively due to induction of an idiotypic antibody cascade. HAMA titer remained significant in multivariate analyses, correlated negatively with the number of previous treatments, and seroconversion was directly related to pretreatment absolute lymphocyte counts. These observations have potential significance for the management of patients with cancer, specifically B-cell malignancies. It is to be hoped that they will be confirmed and elaborated upon by others in prospective studies.

Conflict of interest

The authors declare that no conflicts of interest exist.

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