Improved Radiolabeled Monoclonal Antibody Uptake by Lavage of Intraperitoneal Carcinomatosis in Mice

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The effect of peritoneal lavage with saline on tumor and systemic uptake of intraperitoneally administered tumor-specific (^{131}I-5G6.4) and nonspecific (^{125}I-UPC-10) radiolabeled monoclonal antibodies was evaluated in a nude mouse model of human intraperitoneal ovarian carcinomatosis (IP3 model). Peritoneal lavage at 2 or 6 hr postintraperitoneal antibody injection significantly improves intraperitoneal tumor/nontumor uptake ratios of specific antibody apparently by limiting systemic exposure to antibody. This enhancement tends to be more dramatic if lavage is performed within 2 hr, rather than 6 hr, of intraperitoneal antibody administration, though both times result in significant improvements in target/background ratios over no lavage. Twenty-four-hour tumor/nontumor ratios for specific antibody 5G6.4 generally are 1.5-fourfold higher following lavage than those achieved in control animals, without decreasing absolute tumor uptake of specific radiolabeled antibody. By contrast, nonspecific antibody UPC-10 binding is lower in tumor and normal tissues following lavage, with no lavage-induced improvement in tumor/nontumor ratios seen. Peritoneal lavage is a simple method to allow for specific antibody binding to accessible intraperitoneal tumors yet to limit systemic exposure thus increasing the therapeutic margin. This method may have considerable applicability in the enhancement of intraperitoneal immunoconjugate delivery to intraperitoneal tumors.

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The use of radiolabeled antibodies as diagnostic or therapeutic agents is hindered by the relatively low target/background ratios and absolute tumor delivery achieved following i.v. administration (*1*). While a variety of methods have been proposed to deal with this problem including computerized background subtraction (*2, 3*), antibody fragmentation (particularly using F(ab')$_2$) (*4, 5*), and antibody hapten conjugates (*6*); for localized diseases, such as those limited to the lymphatics or body cavities, the possibility of regional antibody delivery exists, which potentially can circumvent many of the problems of i.v. antibody delivery (*7, 8*). Two malignancies that commonly are limited to the peritoneal cavity include ovarian and colonic cancer.

Intraperitoneal delivery of monoclonal antibodies results in significantly higher exposure of the peritoneal cavity to radioantibody than does intravenous administration (*9*). This regional delivery advantage translates to superior specific monoclonal delivery to isolated ascites cells postintraperitoneal injection, and high solid tumor/blood ratios soon after intraperitoneal injection (*10, 11*). This can also translate to higher absolute tumor uptake and less systemic exposure at early times postinjection for intact tumor-specific radiolabeled antibody (*12–14*). At present, better quantitative results have been seen in patients with i.p. delivery in colon cancer than in patients with ovarian cancer (*11, 12*).

Following i.p. antibody injection blood levels of radioantibody eventually rise due to absorption. With high i.p. doses, this may result in blood antibody levels that could result in toxicity (*15*). This systemic uptake may limit the utility of this approach for high level therapy of isolated accessible i.p. tumor foci. Certainly, however, this systemic delivery may be necessary if tumors are not accessible from the peritoneal space, and in certain instances, the delivery routes may be complementary (*12*).

One approach to limiting systemic exposure in cases

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where only intraperitoneal tumor (accessible from the peritoneal cavity) is present, would be to rapidly clear from the blood the radiolabeled antibody that has left the peritoneal cavity. We have demonstrated the feasibility of this approach in a nontumor bearing animal system through the use of systemically-administered polyclonal anti-mouse antibodies (*16*). We hypothesized that a similar reduction (or lack of rise in) blood radioactivity levels might be seen if the peritoneal cavity is lavaged with saline postintraperitoneal injection. While there would be a rapid drop in the peritoneal fluid radioactivity level, we hypothesized that specific antibody would be firmly attached to intraperitoneal tumor, and that only nonspecific binding would drop, improving tumor/background ratios. Lavage of radioactive albumin from the peritoneal cavity has been successfully performed in humans and lavage following i.p. injection of monoclonal antibodies in humans has briefly been described (*13*, *17*).

The present study was performed to determine whether peritoneal lavage would limit the systemic exposure to radioantibody, yet maintain intraperitoneal tumor uptake of specific antibody given intraperitoneally in a system with intraperitoneal tumor present (HTB77 IP3 ovarian cancer model) (*14*). The concept explored is one of regional (i.p.) delivery of specific antibody to the regional (i.p.) tumor at high concentration, allowing it to bind, and then removing the unbound antibody to prevent unwanted systemic and peritoneal exposure to radioactivity.

METHODS

Antibodies

5G6.4 is a murine IgG2a kappa and binds to most ovarian cancers (*18*). It localizes specifically when labeled to ovarian carcinoma xenografts (*14*, *19*). UPC-10 is a murine IgG2ak myeloma protein without known specificity (Bionetics, Inc., Charleston, S.C.). Generally, 100 μg of purified antibody are labeled using the Iodogen method (Pierce Chemical Company, Rockford,) by reaction with 1 mCi of radioiodine (ICN, Inc.) with 60–80% efficacy of incorporation (*20*). Separation of free from bound iodine is through the use of anion exchange chromatography. Immunoreactivities are measured by a 1-hr direct cell-binding assay to HTB-77 ovarian carcinoma target cells (ATCC) (*21*).

Animal Model

The HTB-77 IP3 model is a model we have developed of human intraperitoneal ovarian carcinomatosis that grows well intraperitoneally in the nude mouse and mimics human ovarian carcinoma (*22*). Athymic Swiss Nu/Nu mice first receive 0.5 cc of pristane i.p. (Aldrich Chemical Company, Milwaukee, WI). One week later, they are innoculated i.p. with 10 million HTB77 IP3 ovarian carcinoma cells. Small tumors grow and attach to bowel, peritoneum, and invade the diaphragm (Fig. 1). The mean tumor size in this study was ~ 0.4 g.

Peritoneal Lavage

The study was divided into two parts, an initial feasibility study, with kill time immediately after lavage to determine the completeness of lavage, and a later study allowing the animals to survive nearly 24 hr postlavage. In the first part of the study, two groups of four nude mice, each with HTB-77 IP3 tumors, were injected intraperitoneally with 0.5 cc of a dual-label mixture composed of 9 μCi of iodine-131 (^{131}I) 5G6.4 and 13 μCi of iodine-125 (^{125}I) UPC-10. The experimental animals were lavaged four times with 2 cc of saline/wash beginning at ~ 1.75 hr following intraperitoneal antibody injection. The animals were injected i.p. with saline and then the peritoneal cavity, after allowing for brief mixing, was drained in the prone position while the mouse was suspended by the neck and tail. Dose calibrator readings on the whole animal were performed before and after each lavage. The multiple lavages were completed by 2.4 hr following antibody injection. The control and experimental mice were then killed with tissues and fluids weighed and counted.

In the second portion of the study 32 HTB77 IP3 bearing nude mice were studied to determine if systemic exposure was lessened by lavage, whether early or later lavage was superior,

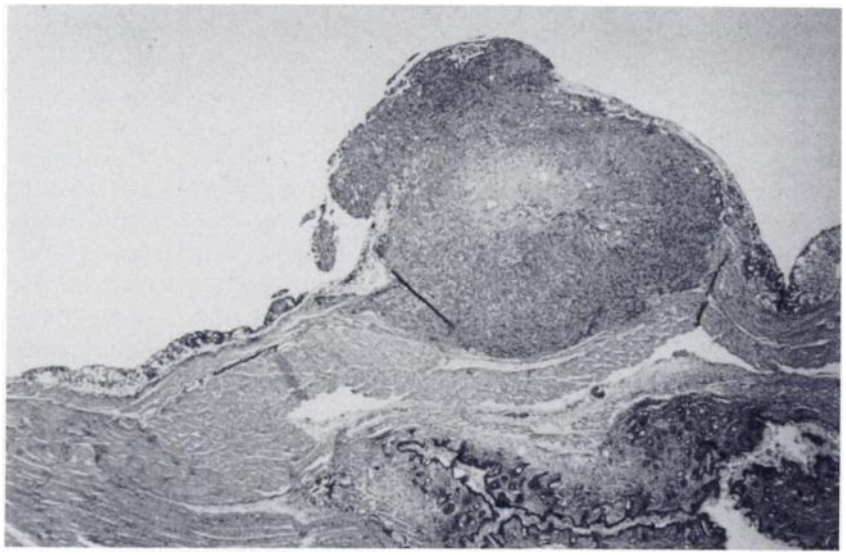

FIGURE 1
Microscopic section demonstrating a focus of HTB77 IP3 ovarian cancer at the peritoneal surface.

and what the effect was on longer-term tumor uptake. Each animal received ~ 10–15 μCi of ^{125}I UPC-10 (irrelevant antibody) and 5–30 μCi of ^{131}I 5G6.4 (specific antibody) intraperitoneally in 0.5 cc as a dual-label mixture. The control group had no lavage, one experimental group had lavage performed at 2 hr postinjection, and the other experimental group had lavage at 6 hr postinjection. No anesthesia was used during the lavage. The lavage was performed by first draining the peritoneal cavity of any ascites, and then washing successively with 2 cc saline washes. After each saline wash, the animals were allowed to ambulate briefly before drainage was done. Thus, a total of five removals of fluid from the peritoneal fluid were performed. The animals were killed at 24 hr postinitial antibody injection. Tissues were weighed and gamma counted at the ^{131}I and ^{125}I channels (with correction for decay and spillover) with percent kg injected dose/g calculated (*23*) (% kg injected dose is % injected dose/g times the animals' weight in kg). Due to the large number (*32*) of animals studied, this work was performed with two different groups of tumor-bearing mice (one with smaller i.p. tumors, mean 0.06, and one with larger i.p. tumors, mean 0.78 g). Statistical analysis was by ANOVA and the Student's t-test.

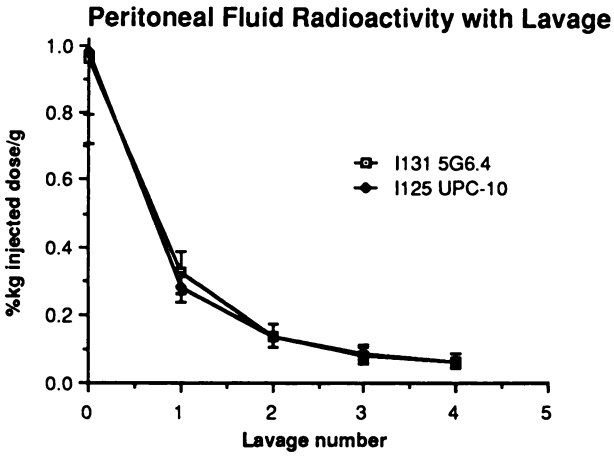

FIGURE 2
The decline in peritoneal fluid radioantibody levels in tumor-bearing mice with successive lavages is shown. Both specific and nonspecific antibodies decrease at comparable rates. The saline lavages are 2 cc in volume, withdrawn with a large bore needle.

RESULTS

In the feasibility study (eight animals-Table 1) in which animals were killed 2.4 hr following intraperitoneal dual-label antibody injection, it was observed that the lavage process could be performed easily. The drop in specific and nonspecific peritoneal fluid radioantibody levels with each successive lavage is shown graphically in Figure 2, which indicates that the drop in peritoneal fluid activity is large with the first two washes, and that further drops with successive washes are less marked. Overall, the drop in intraperitoneal fluid radioantibody levels is quite substantial, and by the final wash a nearly 16-fold drop in radioantibody levels in the peritoneal fluid is observed. The drop in whole-body activities by dose calibrator was also substantial, with post final lavage activity 51 ± 3% of pre-lavage values ($p < 0.0005$).

TABLE 1

	[^{131}I]5G6.4	[^{125}I]UPC-10
Controls		
Tumor i.p.	0.132 ± 0.018	0.135 ± 0.016
Thigh muscle	0.0281 ± 0.001	0.0248 ± 0.003
Blood	0.123 ± 0.021	0.175 ± 0.045
Liver	0.056 ± 0.008	0.042 ± 0.007
Lavage		
Tumor i.p.	0.156 ± 0.026	0.096 ± 0.015
Thigh muscle	0.023 ± 0.002	0.023 ± 0.015
Blood	0.146 ± 0.017	0.225 ± 0.019
Liver	0.075 ± 0.006	0.049 ± 0.003

Effect of lavage (begun 1.75 hr postintraperitoneal dual-label antibody administration) on the uptake of specific and nonspecific antibody with kill time immediately following final lavage (2.4 hr): expressed as % kg injected dose/g ± 1 s.e.m. (n = four animals/group).

Tissue sampling in the feasibility study showed that there was a higher tumor/blood ratio with tumor specific antibody 5G6.4 at 2.4 hr postinjection than with nonspecific antibody UPC-10 in the control group. However, there was a drop in the nonspecific antibody uptake to tumor following lavage, with a low nonspecific tumor/blood ratio postlavage, with little change in the binding of the 5G6.4 antibody to the tumor. Thus, greater relative specificity of uptake postlavage is suggested, with loss of nonspecific radioactivity from nontarget intraperitoneal structures. These observations indicated that the retention of antibody at the tumor was due to the specificity of the 5G6.4 antibody (Table 1).

While the above experiments demonstrate the feasibility of peritoneal lavage in selectively decreasing the level of nonspecific antibody binding to the peritoneal cavity, show that lavage can greatly diminish intraperitoneal radioactivity levels, and show there is no decrement in tumor specific antibody radioactivity levels, they only demonstrate acute effects. For this reason the effects of lavage at 2 and 6 hr after intraperitoneal radiolabeled monoclonal antibody injection on tissue radioantibody levels 24 hr after intraperitoneal antibody delivery were studied. These times were chosen, as our kinetic studies of antibody absorption in the nude mouse indicate that with later lavage times there would be much more systemic uptake and less benefit due to lavage (*14*).

The results of these experiments, shown in Tables 2 and 3, demonstrate that a considerable decline in whole body activity (indicated by blood and liver) is seen with lavage at 2 or 6 hr postantibody injection, with no drop on average in specific antibody uptake in tumors in the

TABLE 2
Effect of Peritoneal Lavage with Saline at 2 and 6 hr Following Intraperitoneal Antibody Administration (Dual-Label Mixture of [^{131}I]5G6.4 and [^{125}I]UPC-10) to animals with HTB-77 IP3 tumors, with Kill Time 24 hr After Initial Antibody Installation

	[^{131}I]5G6.4 (Specific)	[^{125}I]UPC-10 (Irrelevant)
Controls		
Tumor i.p.	0.063 ± 0.005	0.063 ± 0.004
Thigh muscle	0.016 ± 0.004	0.036 ± 0.007
Blood	0.072 ± 0.007	0.148 ± 0.009
Liver	0.021 ± 0.002	0.031 ± 0.001
Spleen	0.016 ± 0.001	0.03 ± 0.002
Lung	0.040 ± 0.004	0.083 ± 0.006
2-hr Lavage		
Tumor i.p.	0.061 ± 0.016	0.034 ± 0.002
Thigh muscle	0.005 ± 0.001	0.014 ± 0.001
Blood	0.024 ± 0.003	0.075 ± 0.006
Liver	0.013 ± 0.001	0.02 ± 0.002
Spleen	0.015 ± 0.002	0.018 ± 0.001
Lung	0.014 ± 0.001	0.034 ± 0.002
6-hr Lavage		
Tumor i.p.	0.056 ± 0.006	0.05 ± 0.006
Thigh muscle	0.009 ± 0.001	0.016 ± 0.001
Blood	0.048 ± 0.006	0.190 ± 0.007
Liver	0.012 ± 0.001	0.021 ± 0.001
Spleen	0.015 ± 0.002	0.021 ± 0.001
Lung	0.02 ± 0.002	0.045 ± 0.003

Results: (kill time 24 hr following intraperitoneal antibody injection): expressed as % kg injected dose/g ± 1 s.e.m. (32 animals studied).

Note that with lavage, the normal organ uptake for both antibodies drops significantly versus controls (except for the spleen), as well as for the tumor with UPC-10 (p generally <0.01). With 5G6.4, no drop in tumor uptake is seen with lavage. In the 1-hr binding assay in vitro to HTB-77 ovarian carcinoma cells, <1% of UPC-10 input counts bound, while 30–50% of input 5G6.4 counts bound.

TABLE 3
Tumor/Nontumor Ratios in Control, 2 hr and 6 hr Lavaged HTB77 IP3 Animals

	5G6.4 (specific)			UPC-10 (irrelevant)		
	C	2H	6H	C	2H	6H
Tumor/blood	1.588 ± 0.368	6.28 ± 2.38	2.66 ± .602	0.455 ± 0.031	0.572 ± 0.08	0.453 ± 0.041
		p < 0.05	p = N.S.	p = N.S.	p = N.S.	
		p = N.S.			p = N.S.	
Tumor/thigh muscle	5.69 ± 0.696	18.88 ± 6.80	7.53 ± 0.81	2.949 ± 0.415	3.025 ± 0.244	3.08 ± 0.352
		p < 0.05	p = N.S.	p = N.S.	p = N.S.	
		p < 0.05			p = N.S.	
Tumor/liver	3.48 ± 0.322	5.24 ± 1.42	4.84 ± 0.437	2.03 ± 0.128	1.958 ± 0.141	2.29 ± 0.21
		p = N.S.	p = N.S.	p = N.S.	p = N.S.	
		p < 0.01			p = N.S.	

peritoneal cavity. In the largest tumors the uptakes of 5G6.4 with lavage were slightly lower than in their control group; though even in these, peritoneal lavage enhanced tumor/nontumor uptake. Nontarget 5G6.4 uptakes in the lavaged animals were in general far less than control values (except for the spleen). There was also a significant drop in the tumor and systemic uptake of nonspecific antibody (UPC-10) following lavage in the same system, which was larger than the drop seen when kill time was at 2.4 hr (immediately postlavage) (46% vs. 29%).

The mean specific antibody (5G6.4) tumor/nontumor ratios, shown in Table 3, clearly demonstrate the enhancement of relative tumor uptake of the 5G6.4 antibody by the lavage approach. The enhancement tended to be greater ($p < 0.1$) when lavage was at 2 hr postinjection, though both 2 and 6 hr time points generally showed significant ($p < 0.01$–0.05) improvements in the tumor/nontumor ratios over control ani-

mals (Table 3). mean 2-hr lavage tumor/blood ratios of 6.3/1 are significantly better than would typically be achieved with the intact 5G6.4 monoclonal antibody given intravenously at this time point. UPC-10 tumor/nontumor ratios following lavage versus controls (Table 3) are virtually identical, indicating that the lavage decreases all tissues uptake of nonspecific antibody proportionately. Thus the lavage process is enhancing the specificity of the labeled monoclonal antibody for tumor.

DISCUSSION

The regional nature of disease such as ovarian cancer and some colon cancers, with spread mainly in the peritoneal cavity, should lend themselves well to regional antibody delivery. A variety of pre-clinical and clinical studies have shown this antibody delivery approach to be useful for colon cancer and in some instances in ovarian cancer (*8*, *10–14*). It is also clear that the intraperitoneal approach alone is not the answer for all i.p. tumors because if there is not access of antibody to antigen, then binding may not occur or may be superior by the vascular delivery route (*12*). Results with the HMFG-2 antibody in ovarian cancer in humans have shown that intraperitoneal delivery of that antibody may, in fact, result in less delivery to tumor foci than i.v. delivery (*14*).

Despite these concerns, in our animal model of intraperitoneal human ovarian carcinomatosis, it is clear that peritoneal lavage enhances tumor/background ratios without, on average, decreasing absolute tumor uptake of antibody. The mechanism of this phenomenon most likely is due to binding of antibody to intraperitoneal tumor, followed by removal of non-bound intraperitoneal antibody before it is absorbed and distributed systemically.

Systemic exposure is reduced up to 50% by this maneuver. This enhancement in relative tumor uptake is achieved, on average, without compromising absolute tumor dose of specific antibody. In the larger (0.7 g or greater) tumors, specific antibody uptake appeared to drop somewhat with lavage, but no drop was seen with the 0.06 g tumors and on average there was no statistically significant alteration in tumor binding. The binding of nonspecific antibody UPC-10 to tumor was dropped by lavage, with the drop more apparent at 1 day postlavage than immediately postlavage. This greater drop in the experiments carried to 24 hr than those at 2.4 hr postinjection may be related to ongoing loss of weakly-attached nonspecific antibody over the time of observation. There was no difference between the 2- and 6-hr lavage times for UPC-10.

From these studies it is apparent that through the use of lavage it should easily be possible to increase several-fold the amount of specific radioantibody given intraperitoneally, without increasing systemic exposure over a low i.p. dose without lavage, and thus increase absolute tumor uptake of radiolabeled antibody to small, accessible, antigen positive intraperitoneal tumor foci. Naturally, careful attention would need to be paid to the possibility of bowel radiotoxicity should higher radioantibody doses be administered; however, the cumulative dose to bowel should not be greater than when no lavage is performed. This may be therapeutically valuable as intraperitoneal radioimmunotherapy is superior to intravenous in an animal model of aggressive intraperitoneal adenocarcinoma of the colon we have been studying (*24*). Certainly, for tumor foci not accessible by intraperitoneal antibody delivery (i.e., where vascular delivery is essential, including many large and subserosal lesions), this lavage approach will not enhance antibody delivery as both vascular and intraperitoneal delivery are needed (*12*). It may, however, be possible to combine intravenous and intraperitoneal delivery plus lavage to optimally deliver radioantibody to both types of tumor (*12*). Regional chemotherapy to the peritoneal cavity is most valuable in low bulk disease and it is likely that this would be the case for regional antibody delivery to the peritoneal cavity followed by lavage (*25*).

In conclusion, peritoneal lavage is a simple method to enhance the specificity of antibody binding to accessible, antigen positive, intraperitoneal tumors and to limit systemic exposure. These effects may allow for higher doses of radiolabeled antibody to be given with the result being more antibody reaching the accessible tumors. Since ovarian cancer spreads initially by intraperitoneal dissemination, such an approach seems rational particularly in early disease. Peritoneal lavage, through increasing the therapeutic index, may have considerable applicability in the enhancement of intraperitoneal radioimmunodiagnosis and radioimmunotherapy, as well as in the delivery of other immunoconjugates, though validation of the technique in patients will be necessary.

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