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Robert M. O'Bryan

Robert W. Talley

Michael J. Brennan

Emiliana San Diego

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Experience with radioisotope therapy at Henry Ford Hospital is reviewed here through critical analysis of results with 105 patients having recurrent malignant effusions. It is concluded that intracavitary isotope administration is of significant benefit and adds to the ease of care and comfort of such patients.—Ed.

Critical Analysis of the Control of Malignant Effusions with Radioisotopes

Robert M. O'Bryan, M.D.,* Robert W. Talley, M.D., F.A.C.P.,** Michael J. Brennan, M.D., F.A.C.P.,† and Emiliana San Diego, M.D.

Recurrent effusion is a frequent problem in the management of patients with neoplastic disease. Clarke reported the occurrence of such effusions in 29% of cancer patients.¹ Ultman stated approximately 50% of patients with carcinoma of the lung or breast developed pleural effusions.² When repeated aspirations of the effusion become necessary, the patient suffers not only local discomfort, but also systemic loss of fluid, protein, and electrolytes. In the past 16 years, much has been written about control of effusions with intracavitary radioactive gold (Au¹⁹⁶). Depending upon patient selection and criteria of control, success with Au¹⁹⁸ has ranged from 30% to 90%,³ — with an average of 50% to 65%.⁴ Radioactive phosphorus, as chromic phosphate (CrP³²O₄), also has been used extensively; in 1958 Jacobs⁵ reported 60.9% control of pleural effusion, and 31.2% control of ascites.

This paper describes the experience at Henry Ford Hospital with Au^{198} or $CrP^{32}O_4$ used in 105 patients with malignant effusions. The effectiveness of results in various primary neoplasms as well as relationship of the results to systemic therapy will be discussed.

Material and Methods

The 105 patients included in this review were seen at Henry Ford Hospital during the nine-year period March 1954 through March 1963. The following criteria were required for inclusion in this analysis: Each patient had histological proof of diagnosis, each patient received therapeutic doses of Au¹⁹⁸ or CrP³²O₄, and the patient had to survive at least 30 days to permit evaluation of effectiveness of therapy.

^{*}Associate, Division of Oncology. Dr. O'Bryan was a fellow-in-oncology sponsored by the American Cancer Society training grant CF-1452.

^{**}Chief, Division of Oncology.

[†]Director, Michigan Cancer Foundation, formerly of the Division of Oncology, Henry Ford Hospital.

Patients were selected for radioisotope therapy because of a fulminating course of malignant effusion or poor response to alkylating agents. Thirty-nine patients had been treated with an alkylating agent, with effective control observed in only five patients. This percentage (12.8%) is far below the 60% reported by other investigators^{6,7} and our average (66.7%) in a smaller series.⁸ However, since approximately one third of the patients in this series were known to be resistant to alkylating agents, it must be considered they represent a more difficult group of patients.

Control of effusion was defined as follows: (1) No increase in effusion as determined by radiographic or clinical measurements, with absence of symptoms. (2) Decrease or disappearance of effusion lasting 30 or more days. (3) An increase of fluid requiring either pleural or abdominal paracentesis but once after the instillation of the radioisotope, with no subsequent recurrence.

Cases were classified as therapeutic failures if (1) fluid persisted with symptoms or fluid increased and (2) if the period of effusion control was less than four weeks.

With Au¹⁹⁸, the dose was 150 mc for intra-abdominal instillation and 75 mc for intrapleural instillation; with CrP³²O₄, the dose was 15 mc for intra-abdominal instillation and 7.5 mc for intrapleural instillation. With minor modifications, the technique of Au¹⁹⁸ administration followed that of Rose et al.⁹ CrP³²O₄ was given by direct needle injection. Precautions in disposal of contaminated material were followed at all times. Only five to ten percent of the initial radioactivity of Au¹⁹⁸ remains in the effusion after six or seven days.¹⁰ Patients who received Au¹⁹⁸ were isolated for five days because of the gamma radiation. Exacting precautions were also taken to protect all personnel from possible exposure to alpha and/or beta irradiation. With the use of these methods, there were no significant complications; no personnel exceeded the weekly limit of 100 milliroentgens.

Patients were divided into four major groups according to primary tumor site breast (28), ovarian (25), gastrointestinal (16), and miscellaneous (36). The miscellaneous division was as follows: nine lung; four each of endometrium, mesothelioma, and unknown primary; three lymphomas, and three patients with two primaries; two renal; and one each of liver, thymus, salivary gland, larynx, synovial sarcoma, urinary bladder, and cervix.

Results

The evaluation of results is difficult because of several factors such as: (1) accurate time observations, (2) occurrence of effusions in more than one serous cavity, and (3) patient selection. Sixty of 105 patients (57.1%) had effusion control for periods up to 10 weeks (Table I). Fifteen of the 60 had their effusion controlled for a period of less than 10 weeks. If a minimum of 10 weeks were established as a criterion for 'control', these 15 patients arbitrarily would be considered failures; the percentage controlled then would decrease to a more realistic 42.9%. Multiple cavity effusions were noted in approximately one half of the group of 60 patients. In seven of these

		Total	Group		Group with Cavities	th Multiple* Excluded	
Primary Tumor	No. Pts.	% of 0 4-10 Wks.	Control 10+ Wks.	No. Pts.	% of 0 4-10 Wks.	Control 10+ Wks.	
Breast	28	57.1	35.7	25	52.0	32.0	
Ovary	25	52.0	44.0	23	47.8	39.1	
Gastrointestinal	16	43.8	25.0	15	40.0	20.0	
Miscellaneous	36	66.7	55.6	35	65.7	54.3	
Total	105	57.1	42.9	98	54.1	39.8	

Table I EFFECT OF RADIOISOTOPE IN CONTROL OF EFFUSION IN 105 PATIENTS

*Seven patients excluded from this group.

See text for further explanation.

patients, effusion control may not have resulted from radioisotope treatment as malignant effusions were controlled in both treated and untreated cavities. If these seven patients were excluded, results would be 54.1% of patients controlled for less than 10 weeks and 39.8% controlled for a period longer than 10 weeks. This report is based on the 57.1% rate of effusion control. The following case report illustrates some of these difficulties in evaluation of response.

CASE REPORT

A 55-year-old white male was admitted to the Henry Ford Hospital on June 30, 1963, because of an eight-month history of progressive cough, weakness, anorexia, and weight loss. He had a history of excessive cigarette smoking for more than 20 years. He was found to have pericardial and bilateral pleural effusions. Ten days later, a pericardiocentesis yielded fluid positive for malignant cells. Fluid from the bilateral thoracentesis was also positive. Clinical and roentgenographic search failed to establish a primary site. On July 20th, 7.5 mc of CrP³²O₄ were instilled into the pericardial sac (Figure 1-A). Right thoracenteses were required July 26, 1963, and August 1, 1963 (Figure 1-B). Beginning August 2, 1963, the administration of systemic 5-fluorouracil (5-FU) controlled right pleural effusions as well as cervical node involvement until December 11, when both pleural effusions and cervical adenopathy recurred (Figure 1-C). The pericardial effusion had not recurred.

Subsequent $CrP^{32}O_4$ failed to control the pleural effusion, and treatment with other chemotherapeutic agents was unsuccessful. The pericardial effusion did not recur (Figure 1-D), and the patient expired March 8, 1964. An abdominal postmortem examination failed to reveal the primary site.

1	Tabl	e II	
EFFECT	OF	THERAPY	CITE
ACCORDING	10	EFFUSION	SHE

	ASC	ITES	PLEU	JRAL	PERICA	RDIAL
Primary Tumor	Control/ Total	% Control	Control/ Total	% Control	Control/ Total	% Control
Breast	1/4	25.0	15/24	62.5	0	0
Ovary	12/22	55.5	1/3	33.3	0	0
Gastrointestinal	3/9	33.3	4/7	57.1	0	0
Miscellaneous	5/10	50.0	18/25	72.0	1/1	100.0
Total	21/45	46.7*	38/59	64.4*	1/1	100.0

 $*X^2 = 2.590$

p less than 0.20



Figure 1-A

Chest x-ray taken after bilateral thoracenteses and before pericardiocentesis with instillation of $\rm CrP^{32}O_4$ (July 20, 1963).



Figure 1-B

Moderate recurrence of right pleural effusion, minimal recurrence of left pleural effusion (August 1, 1963).



Figure 1-C

Control of effusion in all serous cavities during control of systemic disease (October 9, 1963).



Figure 1-D

Continued right pleural effusion $2\frac{1}{2}$ months after $CrP^{32}O_4$ instillation in right chest while other serous cavities remain controlled (February 28, 1964).



Figure 2 The duration of isotope-induced control of effusion in each tumor group.

By effusion site, effects of therapy were as follows: 21/45 peritoneal, 38/59 pleural, and 1/1 pericardial. A tendency for better control of pleural effusion was seen in all tumor types except ovary (Table II).

The number of patients to whom each isotope was given and the therapeutic results are presented in Table III. Effusion was controlled in 49/80 (61.3%) of patients treated with Au¹⁹⁸, and in 11/25 patients (44.0%) treated with CrP³²O₄. A better rate of control was noted with Au¹⁹⁸ than with CrP³²O₄ in breast, ovary, and gastrointestinal; however, the number of patients receiving the latter was too small for definitive comparison.

	Comparison o In Cont	able III of Au ¹⁹⁸ and CrP ³² O ₄ rol of Effusion		
	Au	1198	CrP ³² O ₄	
Primary Tumor	Control/ Total	% Control	Control/ Total	% Control
Breast	11/17	64.7	5/11	45.5
Ovary	11/20	55.0	2/5	40.0
Gastrointestinal	7/13	53.8	0/3	0
Miscellaneous	20/30	66.6	4/6	66.6
Total	49/80	61.3*	11/25	44.0*
1.770 1.660				

 $X^2 = 1.663$ p less than 0.20

The duration of isotope-induced control of effusion in each tumor group is shown in Figure 2.

As these were not randomized studies, statistical evaluation is not applicable, but at the dosage employed, Au^{198} would seem preferable to $CrP^{32}O_4$. The average length of control in weeks for patients treated with Au^{194} was 27.0 ± 4.1 ; with $CrP^{32}O_4$ it was 15.6 ± 2.9 (Table IV).

	Comparison of Au ¹⁹⁸ and CrP ³² O ₄ In Length of Effusion Control			
Isotope	Number of Patients	Length Weeks	of Co	ontrol S.E.
Au ¹⁹⁸	49	27.0	::±::	4.1
CrP ³² O ₄	11	15.6	<u>-+-</u>	2.9

T 11 TY

t = 2.340p less than 0.05

Cytologic studies of effusions were made in 68 patients (Table V). Twenty-six of 54 effusions (48%) with positive cytology were controlled, and 11/14 (78.6%) with negative cytology were controlled. This difference is not statistically significant.

	Positive	Cytology	Negative	Cytology	
Primary Tumor	Control/ Total	% Control	Control/ Total	% Contro	
Breast	4/13	30.8	4/5	80.0	
Ovary	5/11	45.5	1/1	100.0	
Gastrointestinal	6/11	54.5	1/2	50.0	
Miscellaneous	11/19	57.9	5/6	83.3	
Total	26/54	48.1*	11/14	78.6*	

 Table V

 Relationship of Control to Effusion Cytology

 $x_{e} = 1.736$ p less than 0.10

 x^2 value corrected for small sample

At time of isotope administration, serum proteins were studied in 22 patients (Table VI). Both serum protein and serum albumin were considerably higher in patients with effusion control than those in whom effusions could not be controlled. Results in g/100 ml were as follows: for patients with effusion control—serum proteins were 6.47 ± 0.26 , and for patients with effusions that could not be controlled — 5.96 ± 0.26 . Respective values for serum albumin were 3.05 ± 0.22 for the group with effusion controlled and 2.47 ± 0.17 for the uncontrolled group.

Sixty-four patients were receiving hormones or chemotherapeutic agents systemically at the time the isotope was given, or were started shortly after administration of isotope. Fifteen of 19 patients (78.9%) experiencing regression with systemic treat-

		Contr	rol (10)	Failure (12)
Total Serum Protein (g %)		6.47	± 0.26	5.96 ± 0.26
	t = 4.250 p less than 0.01			
Serum Albumin (g %)		3.05	± 0.22	2.47 ± 0.17
ũ.	t = 2.120 p less than 0.05			

ment, had effusion control as compared to 25/45 patients failing to respond to systemic treatment (55.6%). However, this is not significant (p < 0.20).

Various time intervals, such as time from diagnoses to onset of effusion and onset of effusion to administration of isotope, were studied in relation to success or failure of the therapy in control of effusions. No significant correlation could be made in any of these time factors.

Discussion

The pathophysiology of malignant effusion has not been defined completely. Serous effusions are in a continuously circulating pool, with turnover rates of 30-70%/hour in pleural effusions¹¹ and 40-80%/hour in ascites.¹² Because of this massive turnover, a delicate balance must exist between inflow and outflow to prevent large daily fluctuations in accumulated volume.¹² Factors modifying inflow include altered sodium and water metabolism, altered capillary and lymphatic permeability, portal hypertension, and tumor cells themselves. Lymphatic obstruction and hypoproteinemia pertain to outflow.

In ascites secondary to cirrhosis, there can be decreased renal plasma flow with increased renin production stimulating aldosterone release,¹³ decreased destruction of aldosterone by liver,¹⁴ or both. In any event, the commonly elevated urinary aldosterone in patients with cirrhosis and ascites¹⁵ indicates that hyperaldosteronism may play a part in the mechanism of ascites. Pituitary ADH apparently is not a significant factor. Other clinical conditions without water retention have a higher ADH activity than cirrhotics with water retention. Furthermore, livers of normal and cirrhotic individuals inactivate ADH at the same rate *in vitro*.¹⁶ Bangham has demonstrated that irritating amorphous glass particles are removed from the peritoneal cavity via the lymphatics much faster than less irritating glass microspheres, and that the inflammatory response provoked by the amorphous particles increased their rate of removal initially, and only later caused their fixation at the site of inflammation.¹⁷ Lahr has stated that fluid accumulation, in itself, is good evidence that permeability of the walls and functioning of the lymphatic system are markedly altered by the presence of tumors.¹⁸ Also, the

malignant cells may produce lactic acid and/or some other metabolite that results in altered permeability of serosal capillaries.¹⁹

Portal hypertension repeatedly has been shown to be a factor in the production of ascites. The elevated intrahepatic venous pressure carries increased intrahepatic fluid transudation.²⁰ Portal hypertension is, however, rarely associated with malignant effusions.

Popper and Schaffner have stated that regenerating nodules in cirrhosis press on the hepatic vein causing ascites.¹⁶ An expanding neoplasm could exert this same pressure. Extensive study with an ascites tumor in rodents showed certain tumor cells to have the capacity to induce production of ascites and the capacity to grow in the ascitic fluid.²¹ This capacity is not dependent solely upon high growth rate and/or a high degree of anaplasticity of the tumor. There seems to be some variable quality of the tumor cell itself that permits this phenomenon.²²

Lymphatic obstruction and hypoproteinemia are implicated in preventing the outflow of serous effusion. T-1824 labeled albumin injected into the pleural cavity of cats and rabbits is removed exclusively by the lymphatic channels.²³ Abdominal lymphatic drainage is mainly via the diaphragmatic²⁰ and hepatic¹² lymphatic vessels. Clarkson has stated that most neoplastic effusions result from tumor implants on the serosal surface, causing obstruction of the subserous lymphatics or venous radicals.¹⁹ Hypoproteinemia, by reducing the colloid osmotic pressure of serum, reduces its resorptive capacity.

Clearly there must be additional factors, as yet undefined, governing the mechanism of effusion. For example, in Meig's syndrome, ascites and hydrothorax are associated with a benign ovarian fibroma. The mechanism of this effusion is not clear; it has been ascribed to (a) peritoneal exudate resulting from mechanical irritation by the hard mobile tumor, (b) change in capsular veins of the fibroma, and (c) active secretion by the tumor. Any mobile nonfunctioning tumor can do same.²⁴

The question is—by what mechanism(s) did radioisotopes control 57.1% of the malignant effusions in this series? The properties of Au¹⁹⁸ and CrP³²O₄ have been described by Beierwaltes et al.²⁵ Beta emission constitutes 90% of the ionizing radiation from Au¹⁹⁸, and is the major source of energy.²⁶ About 90% of the ionization occurs in the first mm of the exposed serosal surface.²⁷ CrP³²O₄ is a pure β emitter with average penetration of two mm in tissue. Consequently, effect on gross nodular implants is minimal.

It is unlikely that the intracavitary placement of isotope could alter sodium and water metabolism. Postmortem studies have indicated that eventually up to 15% of the administered dose may reach liver, spleen, and bone marrow.²⁶ In our experience most attempts to control recurrent malignant effusions with diuretic programs, i.e. sodium and water restriction, thiazides, mercury, steroids, and spironolactone have been unsuccessful. This probably indicates that sodium retention is not a significant factor in malignant effusion.

If altered capillary and lymphatic permeability are significant in the formation of effusion, then submesothelial fibrosis and obliteration of blood vessels supplying the cavity possibly are the mechanisms of control.²⁹ Frequently, postmortem studies of treated surfaces show fibrous thickening;³⁰ and small peritoneal implants, which perhaps evoke serous secretions, have disappeared following intracavitary Au¹⁹³ therapy.³¹

Similar control rates for both positive and negative cytology groups in this study would seem to indicate that free tumor cells are relatively unimportant in evoking effusions. In addition, Stembridge³² has reported that following therapy, malignant cells persist in the peritoneal washing in a significant number of cases, even though there may be control of effusion.

The role of lymphatic obstruction in the production of malignant effusions is obscure. In Raybuck's work with rats, almost total obliteration of the peritoneal lymphatics produced no increase in peritoneal fluid. When intrahepatic portal hypertension was produced, the ascites was three times greater than in rats with portal hypertension alone. Thus, subtotal lymphatic obstruction, alone, probably does not affect serous fluid dynamics; but, obstruction may play a role in the presence of altered physiological mechanisms involved in serous fluid production.²⁰ Clinically, serosal implants producing lymphatic obstructions and serous irritation are common, but not universally seen in malignant effusion. Studying autopsy material of patients whose main findings were ascites, Berner reported that ascites was associated with peritoneal masses in eight patients with ovarian cancer, and in 8 of the 11 patients who had other types of cancer without cirrhosis. In the remaining three patients, however, extensive hepatic metastases were present, but no peritoneal implants were found. In one of the patients with generalized lymphosarcoma, there was occlusion of the portal vein by tumor; in the other, peritoneal implants were found.³³

Until more specific mechanisms are defined for the production of malignant effusions, the mechanism of action of intracavitary isotopes will remain nebulous. Meanwhile, when recurrent effusions in patients with neoplasia present a problem necessitating palliative therapy, intracavitary isotope administration adds significantly to patient care.

Summary

One hundred and five patients with recurrent malignant effusions were treated with intracavitary Au¹⁹⁸ or CrP³²O₄. Patients were selected for radioisotope therapy because of a fulminating course of malignant effusion or because of poor response to intracavitary alkylating agents. Based on clinical improvement for periods up to 10 weeks and on roentgenographic findings, the overall control rate was 57.1%.

Pleural effusions were better controlled than ascites. Au¹⁹⁸ had a better rate of control and a significantly greater length of control than CrP²²O₄. Patients with gastrointestinal malignancy did not respond as well as patients with other primary neoplasms. Similar control rates were seen in patients whose effusions contained demonstrable

tumor cells and those whose did not. Simultaneous systemic therapy of the malignancy with hormones or chemotherapy, plus intracavitary isotopes, did not significantly increase the rate of effusion control over intracavitary isotope therapy alone. At the time of therapy, serum protein and serum albumin were significantly higher in patients with effusion control than in patients in whom effusions were not controlled.

The mechanisms of effusion development in malignancy are not clear but major operative factors probably include serous irritation and partial lymphatic obstruction.

The mechanism of isotopes in control of effusion, though not proved conclusively, probably is based on tumor cell inhibition and mesothelial fibrosis.

Either isotope may be effective in the management of patients with malignant effusion, and if effective adds measurably to the comfort and ease of care of these patients.

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