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ARTICLE

Results of Ovary Tumor Treatment With Abdominally Administered ^{198}Au Evaluated on the Basis of Long Term Follow Up

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In the period between 1959 and 1980 165 patients – previously operated with ovarian tumor – were treated by intraperitoneally administered ^{198}Au in the Oncoradiological Centre of the Uzsoki Hospital. The stage distribution of the 158 patients with common epithelial histology was as it follows: Stage I/A 31; Stage I/B 9; Stage I/C 59; Stage II/A 19; Stage II/B 11; Stage II/C 7, Stage III/A 22. The five year survival result is the next: Stage I/A 90%; Stage I/B 78%; Stage I/C 58%; Stage II/A 26%; Stage II/B 27%; Stage II/C 14%; Stage III/A 18%. From the other 7 patients six had sex cord tumor and one lipid cell tumor. The number of the side effects is in good agreement with the data in literature. The use of ^{198}Au for intraperitoneal treatment of ovary tumors is not contemporary today because of gamma radiation of radiogold, but intraperitoneal radiation treatment should not be forgotten. (Pathology Oncology Research Vol 8, No 1, 54–57, 2002)

Keywords: ovary tumor, intraperitoneal therapy, radionuclide therapy

Introduction

Tumors of the ovary take fourth place on the female cancer-related mortality scale. Before the chemotherapeutic era, the intracavital treatment introduced by Müller in 1950 was a widespread practice applied after the surgical operation that had a decisive role for the future of the patient. In the beginning ^{198}Au, and after 1955 ^{32}P, was used for this treatment.[13,20] The base of the method was the old experience that even in the case of small primary tumor peritoneal dissemination was detected very often and the surgical operation cannot be curative alone.[8,14] Intraperitoneal treatments with ^{198}Au were used in the Oncoradiological Centre of Uzsoki Hospital from 1959.

Materials and methods

In the period between 1959 and 1980 165 intraperitoneal treatments were performed in the Oncoradiological Centre of the Uzsoki Hospital with ^{198}Au macrocolloid. The average age of the patients was 68 (45-84) years. The tumor originated from the right ovary in 56 cases, from the left one in 51 cases, and was bilateral in 58 cases. The histological distribution agrees with the data in the literature. The most frequent was the common epithelial tumor (158) while the sex cord (6) and the teratoma (1) occurred rarely (*Table 1*). The patients with epithelial tumor of the ovary are reported here. The great majority of the patients were Stage I (St. I/A 31; St. I/B 9; St. I/C 59 patients). There were, however Stage II patients (St. II/A 19; St. II/B 11; St. II/C 7 patients) and even Stage III patients (22) (*Table 2*).

The half-life of ^{198}Au is short (2,69 days). The radiation is 90% beta radiation with a mean energy of 0.316 MeV and a maximum energy as high as 0.959 MeV. The energy of the gamma radiation (10%) is 411 keV. The therapentic effect is due to the short range beta radiation (maximum penetration in soft tissue 3.8 mm).[20]

The radiotherapy was applied 10-14 days after surgery. A catheter was inserted into the peritoneal cavity under local anaesthesia by the so called 'blind placement'. The desired homogeneous distribution of the radionuclide was controlled at the beginning by contrast material and later by ^{99m}Tc. The ^{198}Au colloid was instilled together with 500-1000 ml physiological NaCl solution under antibiotic

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Table 1. **Histological distribution of patients treated with surgery and intraperitoneal ^{198}Au**

Histology	*No. of patients*
Common Epithelial Tumors	
Malignant serous tumors	
Adenocarcinoma	140
Malignant mucinous tumors	
Adenocarcinoma	13
Malignant endometroid tumors	
Carcinoma	5
Sex Cord – Stromal Tumors	
Granulosa stromal tumors	
Granulosa cell tumors	3
Thecoma	2
Androblastoma	
Well differentiated	1
Lipid cell tumors	
Germ cell tumors	
Teratomas	1
Total	165

defence. The activity used was as much as 3,7-5,55 GBq (100-150 mCi). The abdominal channel through which the catheter was introduced was stitched with a suture to avoid the outflow of the radionuclide. After the application the patient was told to change her position in the bed every ten minutes for at least two hours to allow homogenous distribution. The patient was isolated for 21 days to prevent radiation exposune to others.

Results

The 5 year tumor free survival in Stage I is 70%, comparable with the survival rate data in the literature (*Table 3*). Cyst rupture occurred in 30 patients among the 59 patients belonging to the Stage I/C: 22 of them lived tumor of free more than 5 years. The 5 year survival data Stage II (24%) and Stage III (18%) patients are very similar. The cause of this, however, cannot be decided unambiguously.

Feelings of discomfort appeared in 76 patients on the place where the catheter was inserted while in 5 patients there was abdominal pain that ended spontaneously (*Table 4*). One patient was operated on acutely because of intestinal perforation. Two patients died during the treatment. Their death was connected only indirectly with the treatment. Metabolic trouble happened to one of them, connected with diabetes mellitus, while the other died because of activation of a ventricular ulcer. Two patients were operated on in the late follow up period because of ileus, but small intestinal obstruction was controlled by conservative treatment in four patients. Chronic enteritis appeared in five patients, while feelings of abdominal discomfort appeared in 14 patients that had no influence on the quality of life as a result of conservative treatment.

Three patients were operated on because of colonic adenocarcinoma 3, 10 and 13 years after the radiogold therapy.

Conclusion

Before the chemotherapeutic era good result could be achieved by intraperitoneal radioisotope treatment of selected patients. The indications of the treatment are as follows: positive peritoneal cytology, the presence of peritoneal micrometastases and capsule rupture. As the therapeutic effect is due to the short penetrating beta radiation, the treatment is contraindicated when a residuum of macroscopic size is present. Retroperitoneal metastatic lymph nodes cannot be treated by this method.[20]

In practice, the use of ^{32}P is more common than ^{198}Au. The cause of this is the penetrating gamma radiation of ^{198}Au that may result in more complications, higher exposure of staff is and the need the patient separate from other patients. Beside these facts the therapeutic effect resulting from ^{32}P can be better because of the higher beta energy (the mean energy is 0,69 MeV) and the longer half-life than ^{198}Au (14,3 days).[5]

Care should be taken to ensure homogenous isotope distribution during the technique. In cases with adhesions hot or cold spots may occur and the complication rate can increase because of over dosage, or the therapeutic effect can decrease as a result of under dosage. A high isotope concentration occurred in the subphrenic lymph nodes[2] that may explained by the lymphatic system of the peritoneum. This plays a positive role with potential therapeutic effect since it has been shown by Piver et al. that for

Table 2. **Staging of patients treated with surgery and intraperitoneal ^{198}Au**

Stage		*No. of patients*
I	A	31
	B	9
	C	59
II	A	19
	B	11
	C	7
III	A	22
Total		158

(Clinical staging and histological classification were performed according to rules proposed by FIGO-1985 and FIGO-1973.)

Table 3. **Actuarial 5-year survival rates for 158 patients treated with surgery and intraperitoneal ^{198}Au between 1959 and 1980**

Stage		*No. of patients/Total patients*	*%*	*Average*
I	A	28/31	(90%)	
	B	7/9	(78%)	70%
	C	34/59	(58%)	
II	A	5/19	(26%)	
	B	3/11	(27%)	24%
	C	1/7	(14%)	
III	A	4/22	(18%)	18
Total		82/158		52%

tumors thought to be Stage I subphrenic metastases are found in more the 10% of the cases.[19]

The question of dose should be dealt with separately. The applied activity was determined in an empirical way.[12] Later efforts were made to determine the absorbed dose. One way of doing this is to determine the absorbed dose of the different organs during dissection of the lost patients at autopsy.[12] Others made calculations in which the extent of the peritoneal surface, the isotope concentration and the thickness of the fluid covering the peritoneum were taken into account.[1] The absorbed dose of the peritoneum and the omentum maius after administration of 3,7-5,55 GBq were determined on the basis of these data to be as high as 40-60 Gy.

Efforts were made to improve the therapeutic results by combining intraperitoneal and teletherapeutic treatment. The results did not vaccord with the expectations and meanwhile the complication rate increased.[10,18]

Our results are somewhat worse (for Stage I/C, II/C) than the data known from the literature.[3,7,11,17] Analysing the cause, we suppose that in many cases the surgical operation was not radical enough. Since most of the treatments occurred in the 60's the technical conditions for properly radical surgical operations were not available and at the same time the close relation between the amount of residual tumor and the survival rate was not emphasised as it is now.[4] At that time the grading was not determined during histological evaluation, so it could not be taken into account when stating the indication. The low occurence of side effects and complications shows, however that the treatments were made cautiously.

Table 4. **Complications of intraperitoneal ^{198}Au therapy for 158 patients**

Acute	*No. of patients*
Discomfort after instillation	76
Pain and abdominal discomfort	5
Bowel perforation	1
Activated ulcus ventriculi (died)	1
Activated diabetes (died)	1
Chronic	*No. of patients*
Ileus	2
Small bowel obstruction	4
Mild chronic enteritis	5
Abdominal discomfort	14

The method of the intraperitoneal radionuclide therapy was simultaneously surpassed by the spread of cytostatic remedies and this is not a result of the better therapeutic efficiency. This is supported by the fact that intraperitoneal ^{32}P treatments are still carried out in several centres in the United States and Europe.[9,21,22]

The appearance of alkylating agents, the platinum derivatives and taxanes has been a breakthrough in the treatment of ovarian tumors. In spite of this, the five year survival results did not improve significantly and they are not too favourable even today.[15] That is why intereste in intraperitoneal therapy. It is, however obviously clear for us that the application of ^{198}Au would be an out-of date method because of the disadvantages mentioned above. However there are new possibilities in the field of intraperitoneal radio nuclide therapy.

Radio-immune therapy is a separate field of intraperitoneal radionuclide therapy. There were strong efforts by those in the radionuclide therapy field to use the possibilities given by immune therapy. Epenetos et. al were among the first in the middle of the 80's who applied tumor specific antibodies labelled with radioactive isotopes with therapeutic intent. The complex compound has two parts of different function: The antibody's task is to recognize the tumor cell with the aim of the tumor specific antigen and to link to it. The other component, namely the radionuclide, ensures the local irradiation. The radioisotopes most often used used for therapy were the following: ^{90}Y, ^{188}Re, ^{77}Lu, ^{153}Sm, ^{131}I and ^{111}In. The number of usable antibodies is growing continuously. It is an excellent idea to carry out tumor specific local irradiation with radiolabelled antibodies. There are, however some problems in its practical use. Because of the heterogeneity of the tumors, the antibodies are not specific enough. Because of the instability of complex compound a great amount of activity is released and through the circulatory system the radionuclide reaches the bone marrow or the organs. This way it causes unnecessary bone marrow toxicity and/or exposure of the healthy tissue. The so called multistage method provides a new possibility. In the first step monoclonal antibody is administered and later, when the free antibodies disappear from the organism, the radionuclide is administered and this connects to the antibody complex compound. The radionuclides remaining free disap-

pears from the organism within a short time. Several encouraging attempts have been made with the radiating ^{212}Bi and ^{212}At. The energy of α particles is higher than that of β particles, and the range of the particles is very short, so they would be ideal for the therapy of micro metastases.[6,9,16,21,23]

Our aim in this paper is to call the attention to this continuously improving method that may influence favourably the survival results the patints having ovarial tumor.

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