

INTRODUCTION OF THE PRODUCTS REAMBERIN AND REMAKSOL FOR REDUCING TUMOR INTOXICATION AND CONCURRENT REACTIONS IN THE COMBINATION THERAPY OF OVARIAN CANCER OF THE THIRD AND FOURTH DEGREE

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In most countries ovarian cancer shows the highest death rate among all gynecological tumors due to its late detection. The lethality of patients with ovarian cancer during the first year after the disease detection exceeds 35%. Over the last decade the platinum chemotherapy was able to increase the five-year survival rate after the optimum cytoreductive surgery only by 3%, from 32 to 35% [8].

As far back as the 80s a whole number of authors [3, 4] showed that patients with the most common ovarian cancer, and in particular, the one forming ascites, usually have considerable immune suppression, symptoms of anemia and intoxication. The liquid peroxidation and antioxidant blood system are inadequate [1]. The combination of ovarian cancer and old hepatitis represent an even larger problem. As a result, treatment of ovarian cancer of the third and fourth degree with high intoxication often remains unsolved in a number of aspects. It is not only necessary to look for an effective anticancer therapy but also for medicine that can reduce the tumor intoxication [2, 5, and 9].

As a rule, ovarian cancer patients of the third and fourth degree have high surgical risk. It is not possible to start with polychemotherapy for a long time, and the frequency of leukopenia increases. We have used Reamberin and, in cases of reduced kidney function, Remaksol, the main component of which is the succinic acid. Their transformation in the human body is connected to the production of energy necessary for cell activity. The capacity of this energy generation system based on the succinic acid is hundreds of times larger than that of other energy production systems. The replenishment of the pool of the Krebs cycle intermediates leads to the increase in the oxygen transport speed, decrease in the hypoxia and endotoxiosis [10].



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THE AIM

of the present work was to study the effectiveness of the drugs Reamberin and Remaksol for reducing intoxication and concurrent reactions which represent the main obstacle in the effective special treatment.

MATERIAL AND METHODS

The assessment of the state and degree of intoxication was carried out among 171 patients and was based on the clinical, functional and biochemical parameters before the surgery, the beginning of the polychemotherapy and 3–4 weeks after its completion according to the recommended ECOG common toxicity criteria [6].

The effectiveness of application of Reamberin (that has a direct influence on the oxidation processes in the Krebs cycle to remove intoxication and tissue hypoxia) was studied among 89 patients (age 42–79) with stage III–IV ovarian cancer with ascites after cytoreductive surgery and during their polychemotherapy according to the FIGO Stage Classification (Group I). Retrospective patients (89) of the similar age and cancer stage were chosen as a control group

Table 1. Comparative data of the intoxication degree, reduction of blood values and status of ovarian cancer patients in the third and fourth degree before treatment

Group	Number of patients	Degree		Patient's Status (ECOG)			Intoxication degree			Degree of the reduction of blood values*			
		III	IV	II	III	IV	II	III	IV	0	I	II	III
1	89	73	16	17	48	24	16	47	26	9	35	26	19
2	82	65	17	15	42	25	13	44	25	7	32	25	18
Total	171	138	33	32	90	49	29	91	51	16	67	51	37

Table 2. Reduction rate of the haematological values before treatment and during polychemotherapy in the group with Reamberin use and in the control group

Reduction rate of hemoglobin	Group 2 (control group)		Group 1 (with Reamberin)	
	Before treatment	During the polychemotherapy	Before treatment	During the polychemotherapy
0 → 115	70	49	76	79
1 – 100 g/L-115	12	19	13	9
2- 80-100 g/L	-	10		1
3– 65-79 g/L	-	4	-	
4- < 65 g/L				
Reduction rate of white blood cells				
9				
0- >4,0 x10	72	56	81	85
1- 3,0-3,9	10	18	8	3
2- 2,0-2,9		6		1
3- 1,0-1,9		2		
4- <1,0				
Total	82	82	89	89

(Group 2). These 89 patients were operated on in the Novgorod regional clinical oncologic dispensary and city hospitals without the application of Reamberin. Remaksol was used for 9 patients with toxic hepatitis during 5 days until the normalization of parameters.

Even the optimal cytoreductive surgery doesn't stop the disease from growing if the adjuvant polychemotherapy is not carried out in time.

The platinum, cyclophosphamide and/or doxorubicine drugs (a strict one-day combination of cisplatin and cyclophosphamide, or cisplatin, doxorubicine and cyclophosphamide) are used as standard treatment methods in the polychemotherapy. These drugs, besides being highly effective, are also nephro- und cardiotoxic, which has to be taken into consideration. In case the anemia values were lower than 100 g/L, the preparation for the polychemotherapy always started with hemotransfusion.

Table 3. Rate of the heart dysfunction before treatment and during polychemotherapy in the group with Reamberin use and in the control group

Rate of the heart dysfunction	Control group		Group 1	
	Before treatment	During the polychemotherapy	Before treatment	During the polychemotherapy
0 – no dysfunction	20	7	18	23
1 – clinically unsuspected dysfunction	19	20	21	21
2 – transient symptomatic dysfunction, treatment necessary	26	32	27	23
3 – correctable dysfunction, rhythm disturbance	17	23	23	22
Total	82	82	89	89

Reamberin, based on the succinic acid, is dissociated under physiological conditions and is called succinate. The capacity of the energy generation system based on the succinic acid is hundreds of times larger than that of other energy production systems. The replenishment of the pool of the Krebs cycle intermediates leads to the increase in the oxygen transport speed, decrease in the hypoxia and endotoxycosis [9].

Reamberin was injected intravenously as a 1,5% solution 1–2 days before the surgery, every day after the surgery (no more than 90 drops per minute during 5–10 days, 400 ml per day) and during each course of polychemotherapy three days in a row (before, on the day of and the day after the polychemotherapy).

The postsurgical polychemotherapy was carried out in both groups in the following combinations: cyclophosphan 750 mg/m² + cisplatin 75 mg/m² or cisplatin 50 mg/m² + cyclophosphan 500 mg/m² + doxorubicine 50 mg/m² every three weeks with pre- and posthydration, up to 2–4 liters.

For the control group, the number of anemia and leukopenia of the first degree cases before the polychemotherapy was 12 (14,6±2,1%) and 10 (12,2±0,9%),

correspondingly. During the therapy the values of anemia and leukopenia, including stage II–III, increased up to 33 (40,2±3,6%) and 26 (31,7±3,2%), accordingly. The values in Group 1 (with Reamberin) before the treatment were 13 (14,6±2,1%) and 8 (8,9±0,5%) correspondingly, and during the polychemotherapy the haematological values practically remained unchanged (anemia of stage I–II – 11,2±1,1% and leukopenia – 4,4±1,6%). The difference in the number of cases and the reduction rate of hemoglobin and white blood cells in the test group in comparison to the control group is statistically reliable ($p < 0,01$).

The rate of the heart dysfunction of stage II–III in Group 1 was observed among 50 patients (56,1±3,7%) before treatment. With the help of Reamberin the full polychemotherapy treatment was carried out, and the frequency of heart dysfunction was reduced to 45 (50,56±3,4%).

The control group with patients having some heart dysfunction of stage II–III showed quite the opposite result during the polychemotherapy: the number increased from 52,4±3,4% (43 patients) to 67,1±4,1% (55 patients), there was a necessity of additional therapy, extension of the period between the polychemotherapy courses or a decrease in drugs. The difference in comparison to the control group is statistically reliable ($p < 0,05$).

One of the parameters for assessing the level of the urinary system disorder is the increase rate of creatinine. The increase rate of creatinine of the first degree (Table 4) is relatively the same for the patients in Group 1 (12 patients – 13,5%) and Group 2 (11 patients – 13,4%).

Only three patients (3,37%) from Group 1 among those being treated with Reamberin before and during the polychemotherapy showed the same increase in the creatinine level. The number of patients with the increased creatinine level (degree I–III) in the control group grew to 34 (41,4%), which in 12 cases (14,6%) resulted in the suspension of the chemotherapy and additional therapy. The difference between the groups is statistically reliable ($p < 0,001$).

Here are some other manifestations of the toxicity among the ovarian cancer patients treated with Reamberin: nausea and vomiting of degree I–II was observed among 24 patients (26,9±2,2%) and was mainly delayed. The corresponding number of patients in the control group (degree II–III) was 45 (59,2±3,4%), 28 of which had acute symptoms (24 hours after the beginning of the chemotherapy) in spite of the fact that 30 minutes before the beginning of the chemotherapy all patients received an intravenous injection of antiemetic drugs (ondancetron 8 mg or granisetron 1 mg).

The dynamics of the postsurgical levels of serum CA-125 (high-molecular glycoprotein that normally doesn't exceed 35 units/ml) before and during the

Table 4. Increase rate of creatinine before treatment and during polychemotherapy in the group with Reamberin use and in the control group

Increase rate of creatinine	Group 2 (control group)		Group 1 (with Reamberin)	
	Before treatment	During the polychemotherapy	Before treatment	During the polychemotherapy
0 – no disorder (upper limit)	71	48	77	88
1 – <1,5 times over the upper limits	11	21	12	2
2 – 1,5-3,0 times over the upper limits	-	11	-	1
3 – 3,1-6,0 times over the upper limits	-	2	-	-
Total	82	82	89	89

Table 5. Dynamics of postsurgical levels of serum CA-125 during polychemotherapy in both groups

Group	Ca-125 level (units/ml)						
	>1000	500–1000	300–500	100–300	35–100	<35	
After surgery	1	2	3	14	31	39	-
	2	5	8	19	37	13	-
After the 2nd course	1		-	2	19	57	11
	2		6	12	38	23	3
After the 4th course	1			-	5	50	34
	2			7	24	38	13
After the 6th course	1					11	78
	2				16	39	27

polychemotherapy has also been researched. According to N.S. Sergeyeva and co-writers (2002), it is an objective predictive factor of the effectiveness of the ovarian cancer treatment. According to the majority of writers, the level doesn't so much depend on the volume of the tumor as on the involvement of the peritoneal mesothelioma.

After the second course of the polychemotherapy with the combination of cyclophosphan+cisplatin or cyclophosphan+doxorubicine+cisplatin the level of the CA-125 was higher than 100 units/ml among the majority of patients, 59 (68,2±4,2%), in the control group and only among 21 patients (23,5±1,9%) in Group 1, which is twice as low than in the control group.

After the fourth course the level of less than 35 units/ml reached the norm among 38,2±2,4% of patients in Group 1, and was lower than that only among 13 patients (17,1±0,94%) in Group 2.

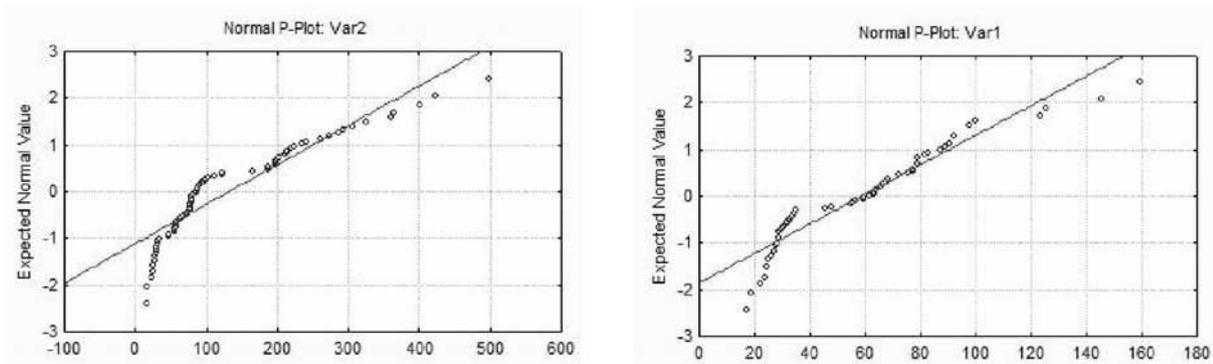


Fig. 1. Comparative data of the disperse analysis of the tumor marker CA-125 after the 4th course of the polychemotherapy in the test group with Reamberin (var. 1) and the control group (var. 2)

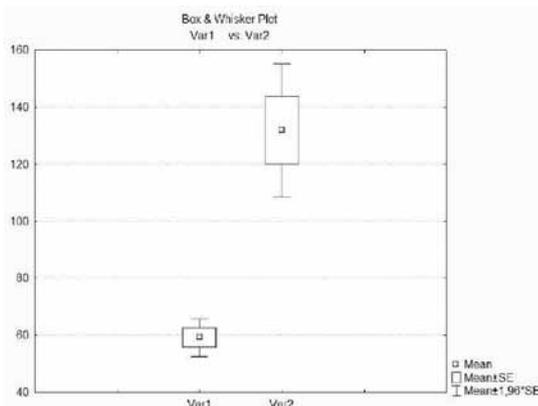


Fig. 2. Levels of the tumor marker CA-125 in Group 1 (var. 1) in comparison to the control group (var. 2)

The statistical analysis of the research results was carried out in the SYS system (Statistical Analysis System, SAS Institute Inc., USA) with the application of the standard algorithms of the variation statistics and in the program STATISTICA 8.0.

The analysis showed that the effects of the decrease in the CA-125 after the second, fourth and sixth course are at level $p < 0,05$.

Thus, the research in the application of the 1,5% solution of Reamberin before and after the cytoreductive surgery and during the following polychemotherapy has shown that Reamberin is a drug that reduces intoxication and side effects of the special ovarian cancer treatment without reducing the anti-tumor effect.

CONCLUSION

1. Application of Reamberin before cytoreductive surgery and during one-day (strict) courses of polychemotherapy creates conditions for reducing tumor intoxication and anemia.
2. Reamberin and Remaksol prevent toxicity during polychemotherapy (using platinum- and doxorubicine-based drugs) without reducing the anti-tumor effect.

3. The decrease in the tumor marker CA-125 is registered within a shorter period of time than in the control group. The statistical analysis shows that the effects of the decrease in the CA-125 after the second, fourth and sixth course are significant at level $p < 0,05$.

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