CYTEMBENA AND CIS-PLATINUM IN COMBINATION FOR ADVANCED STAGE OVARIAN CARCINOMA TREATMENT

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SUMMARY

The Authors studied 10 women suffering from III and IV stage carcinoma of ovary, of whon 8 presented ascites.

To these patients has been administered antiblastic combination constituted by CDDP-MBBA-ADM-CTX for 8 periods of 21 days each.

During the treatment has been administered Tp_1 (100 mg i.m./die).

They report about the first results of the new antiblastic combination.

Carcinoma of the ovary represents gynaecological localization of more difficult access among those of the whole voman's genital apparatus.

It puts great problems of diagnosis and therapy.

The high mortality depends upon the difficulty in the initial diagnosis and even more in the early diagnosis.

In fact 60% of the patients suffering from carcinoma of ovary offers to the clinical observation with disease in advanced phase already (III and IV stage F.I.G.O.).

Thirty-fifty percent of the patients previously treated surgically, with radiotherapy and cytostatic therapy presents relapses ([11]).

The response to the systemic antiblastic therapy is remarkable and sometimes imposing.

Nevertheless the various used protocols are still far from the purpose of a complete and durable remission.

In a previous work ([1]) we have signaled results achieved in treatment of women suffering from carcinoma of ovary by means of administration of 5-Fluoro-Uracile (5-FU) + Adryamycin (ADM) + Ciclophosphamide (CTX) (table 1).

After 44 months from beginning of the therapy, just one woman over 11 patients, equal to 9%, was, and is actually, alive.

No one of the patients presented ascites and all had been operated before the beginning of the antiblastic therapy.

Recently it has been signaled the use of the cisplatin (CDDP), alone or in combination with other antiblastics for the treatment of the carcinoma of ovary ([4, 5]).

For the unsatisfactory results reached precedently by the chemotherapic and irradiating treatment, we have experimented the association of the ADM and CTX with the combination of CDDP and Cytembena (MBBA) that does not result experimented at present.

At the chemotherapical antiblastic combination we have flanked the use of the timostimoline (Tp_1) too.

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Table 1. — *Survival of patients treated with 5-FU + ADM + CTX stage III and IV carcinoma of ovary.*

MONTHS	6	8	12	18	24	30	36	42	44
ALIVE / TOTAL	11/11	11/11	11/11	7/11	2/11	1/11	1/11	1/11	1/11
%	100	100	100	64	18	9	9	9	9

In the present study we report about the first results of the treatment of patients suffering from III and IV stage F.I.G.O. carcinoma of ovary at 18 months from the beginning of the treatment of the first patients by association ADM + CTX + CDDP + MBBA + Tp_1.

MATERIAL AND METHODS

The study was carried out on 10 women affected by III and IV stage carcinoma of ovary; 8 of them presented ascites.

The diagnosis of cancer has been effected by means of cytologic ascertainment on ascitic liquid (fig. 1).

In two women without ascitis the diagnosis has been achieved by cytology study of liquid of peritoneal washing by laparoscopy.

The evaluation of the state before the treatment has been obtained clinically and by means of instrumental ascertainments (scintigraphy, ecography, X rays data) (table II).

The same evaluation has been repeated successively before each period of therapy.

The executed treatment is reported in table III.

The judgments of evaluation of the response to therapy have been the following (table IV):

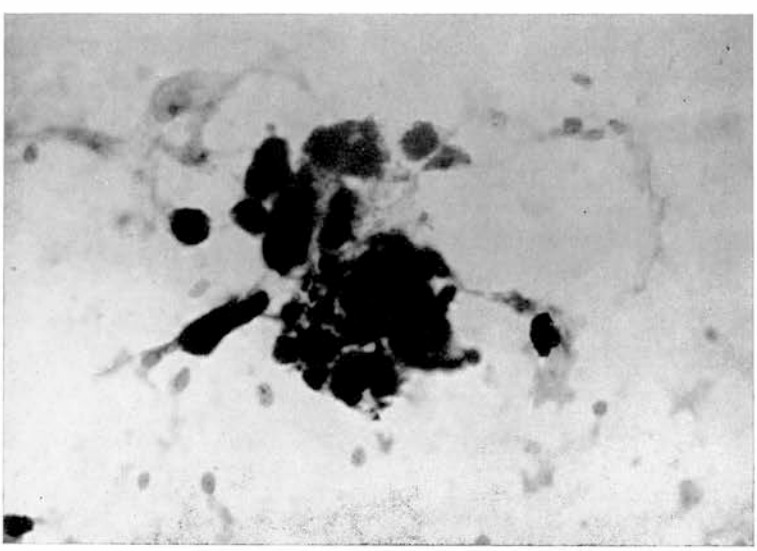


Fig. 1. — Patient G.R. - Ascitic liquid: presence of anaplastic cells.

Table 2. — *Monitoring in antiblastic treatment.*

1)	Physical examination
2)	Gynaecological data
3)	Chest x-rays
4)	Complete skeleton x-rays
5)	Developed urography
6)	Barium enema double-contrast
7)	Barium meal
8)	Abdominal x-rays
9)	Lymphography
10)	Hepatic scinthigraphy
11)	Laparoscopy with eventual biopsy
12)	Abdominal-pelvical ecography
13)	Proctoscopy
14)	Cystoscopy
15)	Cytologic vaginal smear
16)	Fibrin degradation products
17)	LDH/LDH_1
18)	Immunoglobulins (IgG, IgM, IgA)
19)	Fibrinogen
20)	Usual laboratory tests

1) Complete remission (C.R.): disappearance of all the signs and symptoms of disease.

This evaluation has been confirmed from laparoscopy or laparotomy.

2) Partial remission (P.R.): for each measurable lesion, the addition perpendicular diameters must be reduced to 50% or more.

Not appearance of new lesions. The condition must continue for a monthly at least.

3) Quality of life: this evaluation has been effected by means of the Karnofsky's scale.

The treatment has been subdivided in 8 periods of 21 days each.

In the I and II period CDDP (50 mg/mq of corporeal surface) is administered for intravenous way in 1st day and MBBA (130 mg/mq of corporeal surface/die) for rapid endovenous way for the following 20 days.

From III to VIII period CDDP (50 mg/mq of corporeal surface) for endovenous way in 1st day, ADM (37.5 mg/mq of corporeal surface) is administered for rapid endovenous way in 3rd day and CTX (50 mg/mq of corporeal surface/die) for oral administration from 6th day for 15 days.

For all the duration of treatment Tp_1 at daily dose of 100 mg is administered for intramuscular way.

The diagram of the administration of CDDP is the following:

1) patient drinks in 12 hours preceding to administration of CDDP a quantity of liquid equal to 1500 cc;

2) immediately before CDDP infusion furosemide, 20 mg, for rapid endovenous way is administered;

3) CDDP in a quantity of liquids equal to 1.250 cc/mq is administered during 6 hours of infusion.

The liquids are so divided:

50% glucose solution at 5%;

25% saline solution;

25% Ringer's lactate.

4) A mannitol solution, 50 g in 250 cc., is infused in parallel way to administration of CDDP by means of Y collector tube for 6 hours.

The MBBA and ADM are administered for rapid endovenous way while the vein is kept and washed with 250 ml of saline solution.

After the VIII period of therapy, all the patients are submitted to laparoscopy and/or laparotomy.

In this occasion a new evaluation of the stage of disease was made, and a biopsy for histological exame is performed.

In the case of complete remission patients are treated by CTX for oral administration (50 mg/mq of corporeal surface/die) for cycles of 15 days.

This therapy is followed up and eventually the patients are controlled by means of laparoscopy.

In case of P.R. (fig. 3), so as not to permit a large surgical operation, the chemoantiblastic treatment is done « individually » in the limits of the therapeutic approach or passed to other therapy.

In case of patients undergoing large surgical operation, the chemotherapic treatment begins again starting from III period of the therapeutic approach beginning 10 days after the surgical operation.

RESULTS

In the table 5 is indicated the survival of 10 treated patients.

After 6 months from the beginning of the treatment all 10 women are surviving.

After 7 months all are surviving, but 2 have not arrived such period of treatment yet.

After 8 months 1 patient is deceased and 7 are in treatment.

After 10 months 4 are surviving, but 3 have not arrived such period yet.

Table 3. — *Therapeutic approach in advanced carcinoma of ovary associated to ascites.*

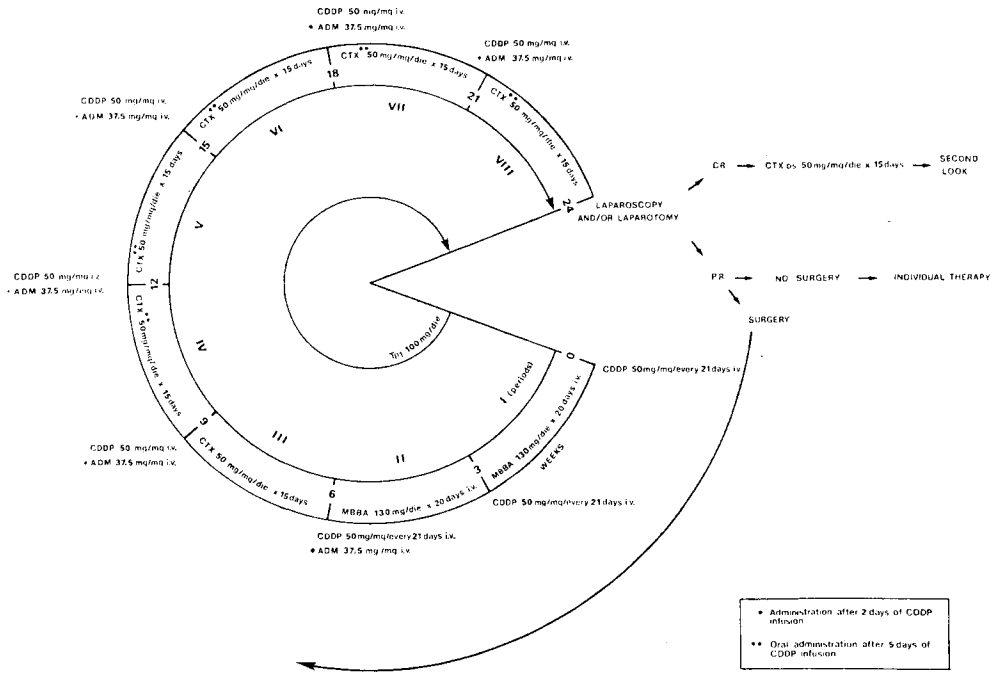


Table 4. — *Evaluation of the response to therapy.*

COMPLETE REMISSION (CR):	Disappearance of all the signes and symptoms of disease, this evaluation has been confirmed by laparascopy or laparatomy.
PARTIAL REMISSION (PR):	For each measurable lesion, the addition of diameters must be reduced to 50 % or more, not appearance of new lesions, the condition must continue for a month at least.
QUALITY OF LIFE:	The evaluation has been effected in according with Karnofsky's scale.

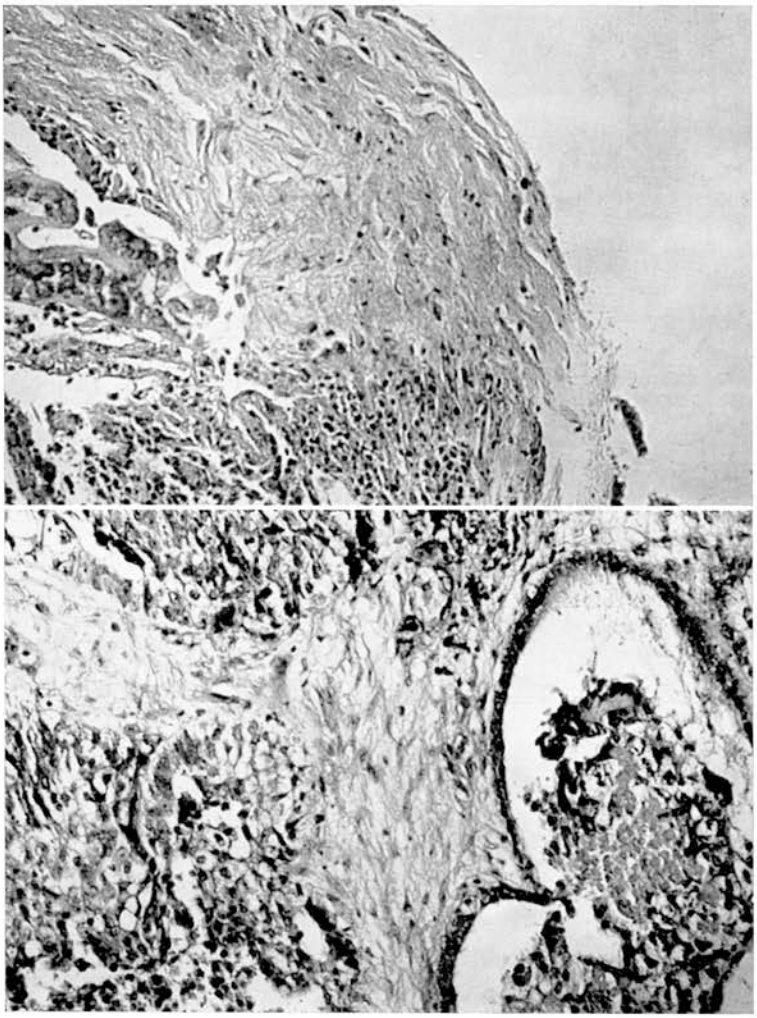


Fig. 2. — Patient G.R. - Biopsy from abdominal hollow: absence of anaplastic cells; presence of connectival fibrous tissue. (H×E 160×).

Fig. 3 — Patient M.M.I. - Biopsy from abdominal hollow: persistence of anaplastic cells of the ovary cystoadenocarcinoma. (H×E 160×).

After 12 months 3 are surviving, only one has not arrived such period.

After 15 months 2 are surviving, one has not arrived such period of treatment.

After 18 months 1 patient lives and one is died.

The patient died at 8th month presented no ascites and one patient at such period has been lost to our control because she was suffering by carcinoma of rectum too, and consequently treated in other institute.

In table 6 are indicated the surgical and antiblastic treatments adopted in relation to the evolution of the disease after the end of 6 months in the first therapeutic cycle.

In this moment all the patients have been submitted to laparotomy or laparoscopy for staging and for biopsy.

Four presented complete remission, five presented partial remission, one was not responsive.

Subsequently 3 are in treatment by our therapeutic approach starting from III period, 2 are in treatment by preservation therapy (CTX + Tp_1) and one has been suffering, as signaled still, by rectum carcinoma.

At 8 months the patients not operated and not responsive at 6 months died.

Of 4 patients in treatment after the the 8th month, one submitted to laparotomy, was in complete remission and is surviving, a second one at 14th month had a recidive, another at 15th month has been submitted to a very large operation and is surviving, another at such period has had a recidive with ascites for which she has been treated with other therapeutic approach (5-FU + ADM + CTX) but at 20th month she deceased.

Table 5. — *Comparison of the survivals of patients affected by stage III and IV carcinoma of ovary and treated by various antiblastic (Bush R. S.:* Malignancies of the ovary, etc., *Edward Arnold, Ed., London, 1979, pag. 77) and therapeutic approach of the study.*

DRUGS	0	6	7	8	10	12	15	18	24	30	36	42	48	months
Melphalan (MPH)		68%				38%		28%	8%	0				
5 FU + Melphalan - Methotrexate (MPH-MTX)		78%				75%		50%		0				
Endoxan (CTX) i.v.		62%				28%		12%	12%	5%	0			
Endoxan (CTX) os		56%				42%		37	10%	10%	5%	5%	0	
(CDDP + MBBA + ADM + CTX) THERAPEUTIC APPROACH (+Tp_1)	(*)	10/10	8/10	7(+)/10	4/10	3/10	2/10	1(+)/10	—					

(+)Exitus of 1 patient

CDDP = Cis - Dichlorodiammine-platinum — MBBA = Bromebric acid (cytembena) — ADM = Adriamicine — CTX = Ciclophosphamide (Endoxan).

(*) Among 10 women in treatment only two died. Number reported to 10 refers to patients in treatment at the indicated month.

In the table 7 are indicated temporal responses to first cycle of treatment expressed in percentual-average.

We valued the quality of life, expressed by means of Karnofsky's scale, ascitic liquid and the neoplastic masses.

For the quality of life we noted an improvement from III period of the treatment for the patients with ascites, while for the 2 patients that had not liquid we had an aggravation.

After the III period ascites disappears completely and abdominal masses suffer a

clear reduction too until to be reduced to the 20% average at the end of 6 months.

For the patients without ascites we had an unsatisfactory response for the reduction of the masses.

Collateral reactions gave no much problems so we didn't stop treatment however none of them required hospitalization.

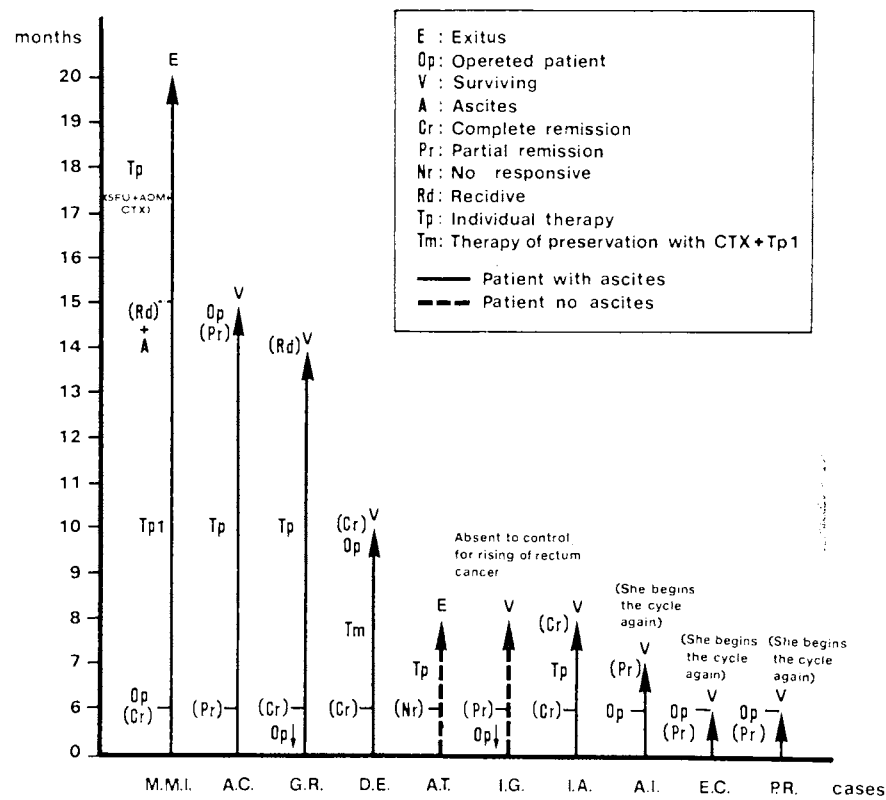
Data are summarized in table 8.

We must underline that it had a big increase of the appetite and a clear improvement of the physical activity always after the third period already.

DISCUSSION

CDDP + MBBA chemotherapic association utilized in the I and II period, in the ascites stage of disease, answers to purpose of utilizing drugs with different point of attack in the limits of cellular cycle (table 9).

Table 6. — *Survival and indiviudal therapy of the treatment after first cycle of chemotherapy.*



CDDP causes inhibition of the DNA synthesis with ties between platinum complex and the helix of DNA (inter- and intrahelix ties) with similar mechanism to that of the alkylating agents ([10]); recent studies should confirm that mechanism of action of the CDDP is independent from cellular cycle (not specific-cycle) ([2]).

Table 7. — *Temporal responses to treatment (means) (CDDP + MBBA + ADM + CTX + Tp1).*

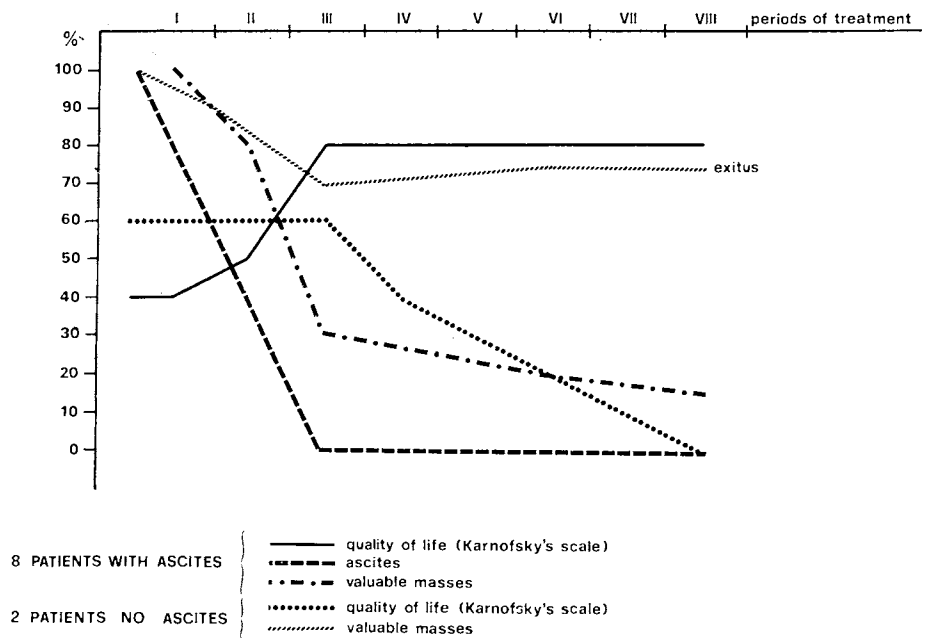


Table 8. — *Collateral reactions noticed in therapy using CDDP + MBBA + ADM + CTX + Tp1.*

1) Nausea and vomiting 100 °/o	(during the infusion of CDDP–ADM and in the following 24 hours)
2) Alopecia 100 °/o	(since third period, after ADM)
3) Decreased white cells count	(such moderate as does'nt require the suspension of treatment)
4) Diarrhoea 20 °/o	(sligth, in the second period of treatment)
5) Nephrotoxicity 20 °/o	(sligth, creatinemie under 1,50 mg °/o)
6) Hepatotoxicity 20 °/o	(variations of the SGOT/SGPT, AP, CPK, γ GT, in rise)
7) Anaemia 80 °/o	(slight, since third period after ADM)
8) Cystitis 40 °/o	(slight, since fourth period)
9) Platelets	(not noticed significant variations)
10) Stomatitis 60 °/o	(slight, after the fourth period)
11) Ototoxicity	(not noticed)
12) Polineuritis	(not noticed)
13) Conjunctivitis	(not noticed)
14) Appetite 100 °/o	(remarkable increased after third period)
15) Dynamie	(remarkable increased after third period).

MBBA, synthetic product of crotonolactone hydrolysis, should act with different mechanism from that of the alkylating agents ([3]), presumably as antimetabolic, and, therefore, specific cycle.

Rationality of the chemotherapic association is based on the presumption of using a drug with action not specific-cycle, able to act on a cellular population in any phase of the cycle, diminishing its entity, and in the daily administration of a second drug with specific-cycle action able of blocking up in GI the cellular growth and of assuring the action also on that quota of cells that eventually reenter in the cycle from G_0, above all in virtue of the persistent haematic concentration of the drug daily administered.

MBBA from III period, with disappearance of ascites, is excluded from therapeutic approach and the polichemotherapic association CDDP + ADM + CTX is utilized in relation with a better therapeutic efficacy of this on solid masses ([1]).

Near to antiblastic therapy we used a drug that stimulates immunitary system.

In fact since time it is known that carcinoma of ovary is a cancer provided of superficial specific-tumor antigens ([8, 9]).

The antigens are in a position to cause an immunitary response of circulating antibodies ([8, 9]) in patients suffering by this tumor.

Many searchers are sure that this response has a role in the evolution of disease.

CDDP has been demonstrated to have capacity of destroying superficial nucleic acids ([6]) that are able to suppress immunologic reactions.

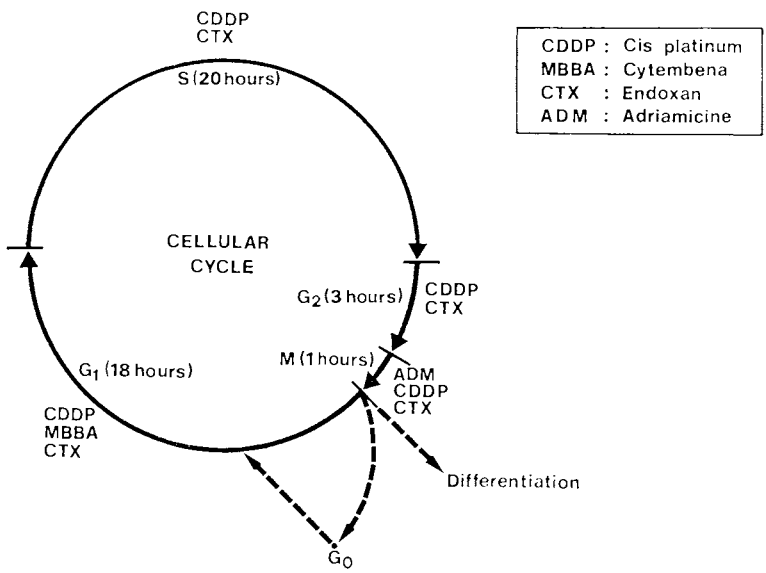
Consequently disappearance of the superficial nucleic acids can contribute, in part, to regression of the tumor ([10]).

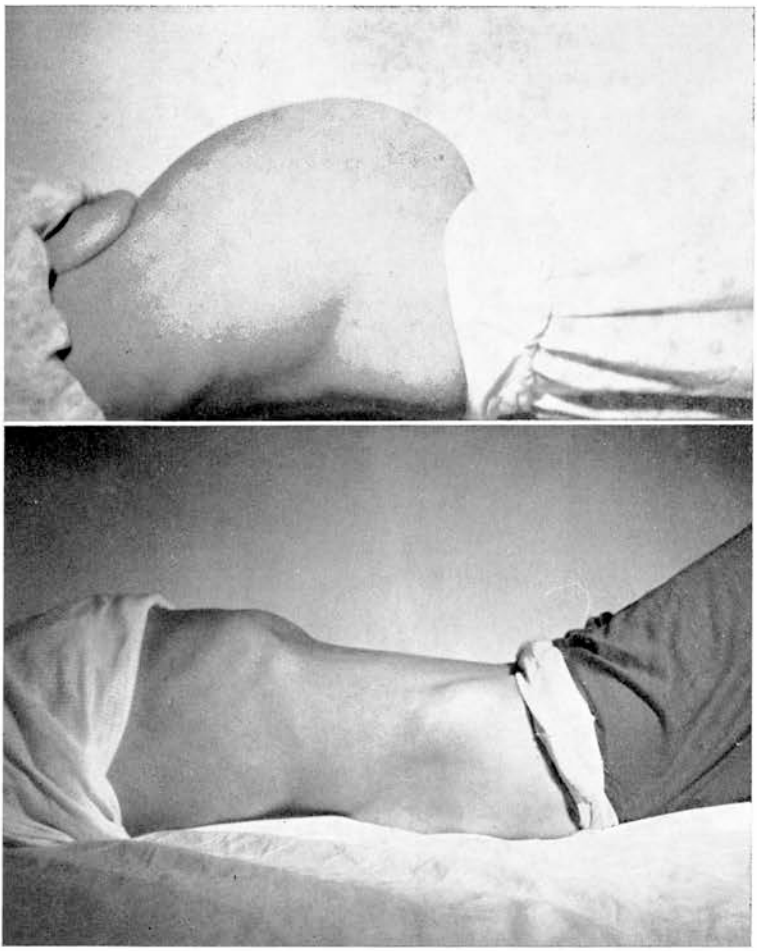
Of course use of the timostimuline is useful for two factors:

1) stimulation of tymo-limphatic system surely depressed by antiblastic therapy;

2) development of immunological res-

Table 9. — *Points of attak of the utilized antiblastics.*





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5

Fig. 4. — Patient A. I. - Abdominal outline showing very large ascites at the beginning of the second period of treatment.

Fig. 5. — The same patient of fig. 4 at the end of fourth period of treatment. The flat abdomen shows complete disappearance of the ascites.

ponse against cancer treated by the CDDP previously.

Because little number of the treated women and brief period of the observation, 2 evident data emerge from our study:

1) after 6 months from beginning of the treatment all the patients that were at III and IV stage are alive.

Data compared with other therapeutic approachs (table 1 and 5) are satisfactory;

2) therapeutic combination adopted for patients with ascites is able to provoke a dramatic reduction of the same (fig. 4 and 5) and of the abdominal masses.

The fact can give to these women the possibility of taking a normal life again.

Therefore reduction of the abdominal

masses and the improved physical conditions permit effectuation of a very large operation if the remission is partial.

In case of recovery of the disease after a period of complete remission, is also possible an operation.

After operation it is possible to start treatment again from beginning so dominating disease in the better manner possible.

In the future we will report about result of the treatment of the studied patients in the present study.

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