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## Medical treatment of trophoblastic disease

by

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Antiblastic drugs in the treatment of trophoblastic tumors are important therapeutic agents ensuring frequent success in modern gynaecology and are often surprising as regards final results.

In the study of trophoblastic tumors numerous reports in the literature indicate both the possibility of a therapeutic association between antiblastic preparations, radiotherapy and surgery, and the possibility of equal success with chemotherapy alone.

The experiences of our unit (<sup>1</sup>) are decidedly favourable as regards treatment with antiblastic preparations alone, combining them with surgery and radiotherapy only in those rare cases of failure.

Chemotherapy in the control of trophoblastic tumors must be applied alone (<sup>2, 3, 4, 5</sup>). This has the ability, in many patients, to prevent the evolution of trophoblastic disease, leading to a final clinical cure (<sup>6, 7</sup>).

The reduction of mortality from chorion-epithelioma, chorio-adenoma and malignant mole observed in recent years, due to the contribution of chemotherapy, is notable in world literature; mortality has been reduced from the 80-100% that was recorded before the advent of chemotherapy (<sup>8</sup>) to about 30% with the use of suitable preparations singly or together with traditional therapy (<sup>7</sup>).

An abundance literature since 1967 shows that the best results are achieved with chemotherapy alone, while combining chemotherapy with surgery, although giving satisfactory results, is less effective. We do not consider that the reservations of various writers on the reliability of the diagnosis of trophoblastic malignancy are sufficient to cast doubts on the real efficacy of chemotherapy.

There is no doubt that these diagnostic difficulties frequently lead to some forms being considered highly malignant, when in fact they are not, and to a

diagnosis of chorion-epitheliomatosis in non malignant histological complexes; but this is not to dispute, in our opinion, the validity of chemotherapy without at the same time disputing the efficacy of surgery and radiotherapy.

In fact this possibility of diagnostic error is not only pertinent in patients treated pharmacologically but also in all patients in whom the other treatments are administered.

Therefore one would have to ascribe to diagnostic error not only all the successes of chemotherapy but also those of surgery and radiotherapy; pursuing this hypothesis, the prognosis would appear bad for the patient actually suffering from chorion-epithelioma whether she is going to be treated with chemotherapy, major surgery or radiotherapy; patients with falsely malignant trophoblastic forms on the other hand should be cured whether they are treated with chemotherapy, with surgery or with radiotherapy alone or in combination.

For just these reasons we must have access, at least initially, to less drastic treatments, but equally capable of success, at least in cases of false malignancy, thus avoiding in these patients the need for major surgery or the serious effects that radiotherapy can have <sup>(10)</sup>.

Only if chemotherapy with appropriate drugs, doses and routes of administration fails, because the form is not sensitive to chemotherapy or because resistance has built up, or for other reasons, must recourse be made with full awareness to other therapeutic measures and, primarily, to surgery <sup>(11)</sup>.

Consequently we advocate and support in the case of trophoblastic tumors the use where possible of chemotherapy alone, resorting to surgery only in particular cases and where the inefficacy of pharmacotherapy is established.

For chemotherapy we recommend the use of Amethopterin which, in our own and in world-wide experience, is undoubtedly the most effective preparation.

Amethopterin must be used in suitable doses together with 6-Mercaptopurine as a result of increased potency due to the synergistic action of the two preparations <sup>(12)</sup>.

Only in cases in which this association, with normal doses and routes of administration <sup>(1)</sup>, shows itself to be ineffective should one resort to other preparations from among Actinomycin-D, Methilhydrazine, Vincalucoblastine etc.

Methotrexate acts with maximum efficacy through its mode of action on the purinic and pyrimidinic synthesis of the nucleic acids, particularly if an antipurinic such as 6-Mercaptopurine is used.

The use of folinic acid as an antidote following overdosage with an antifolate allows sufficient flexibility with this preparation.

With chemotherapy <sup>(9, 10)</sup> in 18 cases of chorion-epithelioma of which 14 were with pulmonary, hepatic, cerebral, etc., metastasis (and of these two teratocorion-epithelioma) we achieved a complete cure in 12 cases. Three of these patients have had subsequent pregnancies.

Often the results achieved in very serious cases were surprising, some appeared miraculous and have left us surprised and almost incredulous!!!

The route of administration of these drugs has great bearing upon the results; we prefer *systemic therapy* with Methotrexate given intravenously or continuous *local therapy by endoarterial infusion*. This latter method has shown itself to be the most effective in patients treated by us.

There are various techniques for this infusion. We have abandoned those, of the extracorporeal circulation <sup>(13)</sup> and of surgical catheterisation of the hypogastric artery <sup>(14, 14, 16)</sup>; of hypogastric catheterisation via the gluteal artery <sup>(17)</sup>

but we always preferred transcutaneous and transfemoral catheterisation of the lumbar aorta <sup>(12)</sup> or selective transcutaneous and transfemoral catheterisation of the hypogastric artery and its branches <sup>(18)</sup>. With this method *direct catheterisation of the uterine, pudendal etc. arteries* is also possible.

The antitlastic drugs can thus act at a maximum concentration directly on the malignant trophoblastic tissues, and with treatment extending into weeks with successive cycles of the drug at a high dosage.

The arteriographic study of symptoms in local endoarterial treatment provides accurate information and differential diagnoses on the benignancy of the forms being examined and treated. Moreover the behaviour of the vascular bed, its possible reduction or modifications in the arterovenous shunts during local chemotherapy show the efficacy of this treatment.

The arteriography of arterovenous shunts and large blood lakes perfused with the contrast medium are diagnostic for chorion-epitheliomas, whilst in vesicular moles both on the full uterus (with the vesicular mole still in situ and living) and on the empty uterus (after its expulsion or removal) arteriographic pictures are typical of a symmetrical vascularisation of the two halves of the uterus.

Histological pictures of vesicular moles, in spite of numerous classifications <sup>(20)</sup>, do not permit a accurate prognosis of their future development. The frequent development towards chorion-epitheliomatosis leads us to consider chemotherapeutic treatment necessary as prophylaxis against the long term possibility of malignancy.

We put forward this treatment because the incidence of chorion-epithelioma after vesicular moles is increased and because systemic intravenous chemoprophylaxis in restricted doses is free of side effects.

Amethopterin acts upon the trophoblastic epithelium, whether it is normal, with a mole or with a chorion-epithelioma; and as a prophylactic it destroys these trophoblastic elements which have not been eliminated by curettage or have remained in the circulation and which because of their structural independence or factors unknown can be subject of successive malignant degeneration.

In *chemoprophylaxis of the vesicular mole* the use of chemotherapy occurs when the mole has already been expelled or removed; in *chemotherapy of the vesicular mole* on the other hand the mole is still in the uterus and control of the condition is left to pharmacological treatment.

We have studied and propose this kind of pharmacological therapy of the vesicular mole when this is still alive, functioning and growing in the uterus <sup>(1)</sup> <sup>(10)</sup>.

With this treatment the vesicular mole is inhibited, restricted and circumscribed in its development and growth.

The dosage of antifolics must be in direct proportion to the quantity of trophoblastic tissue, that is to the volume of the mole and its development and must be administered continuously until the mole is dead, its volume reduced, there is evidence of necrosis of the chorion epithelia, disappearance of the hydrops of the villus and its spontaneous expulsion with minimal haemorrhaging, so that there is no necessity for curettage, or hysterectomy, which in the past has been the only valid therapy in this complaint.

Our experience in several dozen cases of live vesicular moles treated with chemotherapy alone right up to their spontaneous expulsion from the uterus enables us to recommend this method because it is really simple and free of side effects.

We regard actually superfluous curettage of the uterine cavity after the expulsion

of the mole because we believe that only chemotherapy, in chorial invasion of the miometrium, will destroy all the trophoblastic structures and tissues.

In conclusion therefore we maintain that:

1) Chemotherapy must only be undertaken in cases of trophoblastic tumors, provided that drugs, doses and routes of administration are suitable; surgery only in cases of failure with chemotherapy.

2) With vesicular moles, irrespective of the group to which they belong, chemoprophylaxis should be carried out systematically.

3) In cases of vesicular mole, chemotherapy must be used while the mole is still in the uterus, alive and functioning, because with infusion, even simply with Amethopterin intravenously, the death and spontaneous expulsion of the mole follows, thus sparing the patient bloody and dangerous surgery.

### SUMMARY

The chemotherapy of chorion-epithelioma, the choice of the route of administration of antitlastic drugs, the arteriographic study of trophoblastic tumors, the chemoprophylaxis and chemo-therapy of the vesicular mole are reviewed in respect to their actual indications long term results.

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