ANTIBLASTIC CHEMOTHERAPY AND REPRODUCTIVE LIFE

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Summary: In the present work the Authors, on the basis of most recent literature have tried to show some general outline with regard to the effects of antiblastic chemotherapy on the " ovarian function " in patients of pre-puberal and fertile age, understood that this would mean complex interference between endocrine and gemetogenic; they have besides faced the problem of the gestational capacity of such patients.

Notable difficulties have derived from the fact that the data in Literature are often non-comparable among themselves and, at times, discordant.

However, although they have been unable to reach unequivocable conclusions, they hope to have made some practical contribution to those who, ever more often, find themselves having to face such problems.

INTRODUCTION

In recent years there has been increasing use of chemotherapy in the treatment of neoplasia, also thanks to the data obtained through an impressive number of controlled clinical studies which have shown the part antineoplastic drugs play, often determinant, and not only complementary to other types of therapy. From this derives the involvement of patients in fertile age or even premenarchal, and the question arises spontaneously to ask ourselves what effect this type of therapy may have on the "ovarian function", understood in the fullest sense of the term, that is, as a complex interference between endocrine and gametogenic functions.

While with regard to possible teratogenic damage through administration of antineolpastic drugs in pregnancy, there have been numerous and noteworthy studies to be found in Literature, concerning the effects of antineoplastic drugs on reproductive life as a consequence of their action on ovarian activity, yet these are rather rare and often make difficult reading.

Although in the first period of their use antineoplastic drugs, even in experimental protocols, were significant only as complementary therapies and very often just as palliative in the following periods chemotherapy assumed a fundamental role in the complete cure of some neoplasias. This fact, accompanied by the ever more frequent use of chemotherapeutic regimes, has led to the closer examination of the long-term outcome of such therapies in regard to the reproductive life of the patient. From this arise many questions and problems with which the specialist must be prepared to deal: how, for example, will puberty develop in girls who, as children suffering from leukemia, had been treated by intensive cycles of chemotherapy, including some highly toxic drugs? What alterations are to be expected as to the duration and rythm of a normal menstrual cycle? Is it right to expect an exhaustion of ovarian function as prefiguring a picture of premature menopause? What will be the gestational capacity of such patients, it being plausible to hypothesise mutagenic modifications at the ovarian level?

The aim of the present work is simply that of giving, where possible, answers to these questions on the basis of a study of the most recent Literature; and this with the aim of going more deeply into an extremely complex subject from which should emerge information of a practical order, directed towards giving indications as precise as possible.

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THE AIM OF THIS WORK

As we have already said, we prefigure the study of "ovarian function" understood in the widest sense of the term: however, rather than as a speculative contribution on the data in Literature, we are aiming at more practical ends, that is, attempting to give some guidance to those who, in increasing numbers, turn to gynecologic oncologists to know what attitude to take when facing patients who are undergoing or have undergone antiblastic chemotherapy and who have or may have to face alterations of their physiological reproductive activity. In practise this means being able to obtain and up-date our knowledge, in order to be able to advise patients regarding problems of ovarian activity in a general sense, to advise for or against pregnancy, many times feared or refused, but also often sought with intensity of hope.

Then again, it is necessary to make things clear, and righ to explain them to this particular type of patient, in order to remove excessive fears which, in the light of ever more frequent studies, are at times unjustified. At the same time it is worth while recognising the still preliminary character of many clinical observations, also for avoiding the creation of anxieties or hopes which would be difficult to realise.

In order to arrive at all this we have studied all the relevant Literature that has appeared in the last few years, and we must admit at once that we encountered considerable methodological difficulties when we tried to summarise all the data collected into a few simple schemes for rapid reading. In fact the most serious problem was presented by the comparison of case series in which were reported the use of different drugs, singly or in the most varied associations, for the therapies of neoplastic pathologies or otherwise; besides, and this is almost the rule, the dosages of each drug, where indicated, were widely varied, the duration of treatment too often unspecified, and again, generally, the time that elapsed between the end of the treatment and the onset of symptomology was not made clear.

In conclusion, as many Authors have shown, it is necessary to consider carefully the effects on endocrine and gametogenic functions of each individual pathology itself, independently of the therapy established.

From this derives the extreme difficulty of assigning to any single drug or association the pathogenic responsability for a symptom; thus, too often we fall into error if we try to attribute to any one antiblastic chemotherapy a precise cause and effect relationship, and for this reason what we shall report must be considered as having an exclusively indicative meaning, in a clinical field where, as we know, much remains to be clarified.

We have subdivided the data collected into three groups – thus: 1) relation between antiblastic drugs and puberty; 2) relation between antiblastic drugs and alteration to the menstrual cycle; 3) relation between antiblastic drugs and reproductive capacity.

RELATION BETWEEN ANTIBLASTIC DRUGS AND PUBERTY

As can be seen in table 1, the most frequent pathology requiring the use of antiblastic drugs in the prepuberal and puberal period is represented under the heading "lymphomas - leukemia", and by chronic glomerulonephritis. From the analyses of data we observed that the use of cyclophosphamide alone in cases of glomerulonephritis ([6, 7, 8]) does not alter puberal development; on the other hand, in the case of lymphomas or leukemia, with the use of polychemotherapy including vincristine, prednysolone and/or methotrexate, some alteration in puberal development is to be expected, understood as a percentage of cases varying from 20 to

Table 1. – *Relation between antiblastic drugs and puberty.*

	Lymphomas - Leucemias	*Chronic glomerulonephritis*
Normal puberty	100%: Polichemotherapy non spec. (1) 80%: Pr., VCR, MTX, 6MP and/or CF (2) 100%: M, VCR, P, Pr. (3) 94% if in prepuberal age: Pr., VCR, MTX, 6MP (4) 67% if in puberal age: Pr., VCR, MTX, 6MP (4)	100% CF (6, 7, 8) 100% Clb., Pr. (9) 80% VCR, MTX, 6MP, S. (1)
Altered puberty	60%: CF (5) 20%: Pr., VCR, MTX, 6MP and/or CF (2) 6% if in prepuberal age: Pr., VCR, MTX, 6MP (4) 33% if in puberal age: Pr., VCR, MTX, 6MP (4)	20% VCR, MTX, 6MP, S. (1)

Legend: Pr.: Prednysolone; VCR: Vincristine; Methotrexate; 6MP: 6 Mecaptopurine; CF: Cyclophosphamide; M: Mustine; P: Procarbazine; S: Steroids; Clb: Chlorambucil.

60% ([1, 2, 3, 5]). Schilsky ([4]) in particular, underlines the importance of the age factor in the patient as determining the alterations in puberal development in the sense that the precocity of pharmaceutical interference related to the onset of puberty and the alterations of puberty itself are inversely proportional between themselves.

RELATION BETWEEN ANTIBLASTIC DRUGS AND ALTERATIONS IN THE MENSTRUAL CYCLE

With regard to the therapies used in lymphomas of the Hodgkin type or of leukemias, the most widely used scheme is MOPP (Methotrexate, Vincristine, Prednysolone, Procarbazine; generic alterations in the menstrual cycle are reported with percentages varying from 0 to 49% of cases ([20, 23, 24, 36]), excluding the 100% referred to by Beard ([22]) who had reported only two cases. The observations of Chapman ([23]) should be underlined, according to whom the use of oral contraceptives during chemotherapy proved to have a protective effect on the ovary and, therefore, the estroprogestinic ought to constitute a complementary therapy to antiblastic treatment. In another series of patients Chapman ([28]) studied the effect of the association of meclorethamine, vinblastine, procarbazine and prednysolone; 41% of the patients entered the menopause and anyway 49% complained of more or less prolonged periods of amenorrhea.

Bonadonna ([26]) and Santoro ([29]) observed no alterations of the cycle in women affected by Hodgkin's disease who were submitted to cycles of doxorubicine, bleomycine, vinblastine, dacarbazine.

More serious effects were experienced, however, among patients undergoing various cycles of chemotherapy for neoplasias of the breast; the combined use of adriamycin and cyclophosphamide, or of cyclophosphamide, methotrexate and 5 fluorouracil can induce generic alterations to the hormonal cycle in up to 100% of patients ([16, 17]) causing amenorrhea in 54% of cases ([16]).

Even in this type of pathology an important factor to be considered is the patient's age; Fischer ([15]) and Shalet ([14]) in fact observed that by using an association of Melphalan and 5 Fluorouracil amenorrhea resulted in up to 12% of the patients younger than 34 years of age, while beyond that age 64% of patients were affected.

With regard to patients affected by trophoblastic diseases Rustin and Bagsha-

we ([11]) have emphasised how the use of methotrexate as sole drug determined an incidence of anovulatory cycles equal to 1.7% of the cases observed (tables 2, 3).

RELATION BETWEEN ANTIBLASTIC DRUGS AND REPRODUCTIVE CAPACITY

Regarding the reproductive capacity of patients affected by neoplasias, especially Hodgkin's disease, invasive mole and choriocarcinoma, there are numerous cases in Literature indicating the possibility of pregnancy occurring after the end of chemotherapeutic cycles; besides, as can be seen in tables 4, 5, the outcome of such pregnancies was positive in a percentage of cases varying, according to the Authors, with the type of chemotherapy followed, from a minimum of 58% referred to by Pastorfide ([53]) using methotrexate associated with actinomycin D as treatment for vescicular mole, to a maximum of 87% referred to by various Authors ([50, 51, 52]) who were using methotrexate alone for this same type of neoplasia. Rustin and Bagshawe ([12]) in this context present the results of a study conducted on 315 pregnancies occurring in women previously submitted to cycles with methotrexate as the sole drug. In 77% of the cases the pregnancies had positive results, the rest of the quota ended in abortion which, in many cases, was induced, not spontaneous; no malformations were observed, major or minor.

These same Authors, in another study regarding patients affected by molar neoplasias ([11]) reached the following conclusions: 1) conception is possible with any type of chemotherapy excepting Cis-platinum and Ethoposide; 2) the use of cyclophosphamide is burdened with a high percentage of failure; 3) the association of more drugs reduces the probability of live births; 4) there seems to be no relation between dosages of the various drugs and future fertility; 5) it is, however, possible to notice alterations in fertility and teratogenesis.

CONCLUSIONS

As may be observed from the discussion of the data reported, the use of chemotherapy in patients of fertile or pre-puberal age raises a great number of problems, and often brings the gynecologic oncologist and the woman herself face to face with compelling questions to which it is not always possible to reply with certainty ([55]).

Some schemes or pharmacological associations appear to induce a higher percentage of alterations, even serious ones, to the "ovarian cycle" understood in the widest sense of the term, while other drugs, such as methotrexate, for example, give greater guarantees of success, also in regard to future pregnancies. In this study of ours we have intended giving maximal indications to all those who find themselves in the necessity of giving answers to patients, who, affected by the most varied neoplasias, want to know what the future will be for their menstrual cycle, what possibility they will have of bringing to full-term a pregnancy often much desired, and what probability there may be of harmful effects on pregnancy awaiting them.

As we have said before, it is very difficult to give definite answers just because the data in literature are protean, often non-comparable, and in any case cannot be randomised. Besides, to make any position of absolute optimism or pessimism still more fallacious, there are contrasting indications concerning the use of the drugs themselves.

It seems symbolic to us to report a case described by Schapira ([21]). A girl of 21 years affected by a diffused istiocitic lymphoma was submitted, between February 1981 and October 1982 to innumerable cycles of associations, including the most disparate drugs; bleomycin, cyclo-

Table 2. – *Relation between antiblastic drugs and alteration to the menstrual cycle.*

	Trophoblastic disease			*Neoplastic pathology of the breast*				
	MTX	Act. D	VP-16	Melphalan, 5FU	Polich. with CF	CF alone	CMF	CMF, VP
Generic alterations	0% (10)	/	32% (13)	/	100% (16) 100% (17)	/	87% (17)	/
Amenorrhea	0% (10)	/	32% (13)	12% if ⩽39 aa (14) 64% if ⩾40 aa (14) 7% if ⩽39 aa (15) 22% if ⩾40 aa (15)	54% (16)	94% (18)	50% (17) 100% (19)	100% (19)
Anovulatory cycles	0% (10) 1.7% (11) 1.6% (12)	7.7 (11)	9% (13)	/	33% (17)	/	/	/
Menopause	0% (10)	/	/	/	/	/	/	/

Legend: MTX: Methotrexate; Act. D: Actinomycin D; VP-16: Etoposide; 5FU: 5 Fluorouracil; CF: Cyclophosphamide; CMF: Cyclophosphamide, Methotrexate, 5 Fluorouracil.

Table 3. – *Relation between antiblastic drugs and alteration to the menstrual cycle.*

	Hodgkin's Disease - Lymphomas				*Glomerulo-nefritis*	*Osteo-sarcoma*	*LES Artr. reum.*
	MOPP	MVPP	ABVD	Various associations	Cyclophosphamide	MTX, VCR	CF
Generic alterations	36% [20] 29% [1] 100% [22] 0% [23] 49% [24]	34% [28]	0% [29]	60% [22] Polich., CF	50% [31]	0% [10]	—
Amenorrhea	15% if <30 aa [25] 49% if >30 aa [25] 9% [20] 15% [36] 26% [37] 46% [38] 34% [24] 28% [39] 0% if <30 aa 46% if >30 aa	49% [28]	0% [26, 29]	10 Pz. [30] 1 Pz.: CF, V [30]	50% [32] 8 cases [33]	0% [10]	23% [34]
Anovulatory cycles	—	—	—	—	—	—	—
Induced menopause	57%	41% [28]	0% [29]	1 Pz. [22]	—	—	18% [35]

Lenged: MOPP: Nitrogen Mustard, Vincristine, Procarbazine, Prednysone; MVPP: Chloridrate Mechloretamine, Sulphate Vinblastine, Procarbazine; ABVD: Doxorubicine, Bleomycin, Vinblastine Dacaebazine; MTX: Methotrexate; VCR: Vincristine; CF: Cyclophosphamide; LES: Eritem. Sistemic Lupus; Art. Reum.: Rheumatoid Arthritis.

Table 4. – *Relation between antiblastic drugs and reproductive capacity.*

	Hodgkin's Disease						*Various neoplastic pathologies*
	P	MVPP	MOPP	MTX, 6MP	MTX, 6MP, Act. D 6 Azouridine	Act. D, CF, 5FU	Varied association
Pregnancies (in no. tot. or in %)	no. 1 [40]	no. 1 [41] 7.3% [28]	no. 23 [42, 43, 54] no. 1 [23] 27% [20] no. 30 [37] 29% [38] 7% [28] 8% [26]	no. 1 [44]	no. 64 [45]	no. 1 [46]	no. 116 [47, 48]
Live births	1/1 [40]	1/1 [41]	87% [42, 43, 54] 1/1 [23] 73% [37]	1/1 [44]	70% [45]	1/1 [46]	84% [47, 48]
Malformations	/	/	9% [42, 43, 54] 3% [37]	/	8% [45]	/	/
Interruptions of pregnancy	/	/	4% [42, 43, 54] 27% [37]	/	22% [45]	/	16% [47, 48]

Legend: P: Procarbazine; MVPP: Chloridrate Mechloretamine, Sulfate Vinmblastine, Chloridrate Procarbazine, Prednysolone; MOPP: Nitrogen Mustard, Vincristine, rocarbazine, Prednysone; MTX: Methotrexate; 6MP: 6-Mercaptopurine; Act. D: Actinomycin D; CF: Cyclophosphamide; 5 FU: 5 Fluorouracil.

Table 5. – *Relation between antiblastic drugs and reproductive capacity.*

	Act. D	VP-16	6-MP	MTX	MTX, Act. D
Pregnancies (in no. tot. or in %)	92% [11]	no. 6 [13]	no. 1 [49]	no. 53 [50, 51, 52] no. 315 [12]	no. 57 [53]
Live births	82% [11]	66% [13]	no. 1 [49]	87% [50, 51, 52] 77% [12]	58% [53]
Malformations	/	/	no. 1 [49]	6% [50, 51, 52]	19% [53]
Interruptions of pregnancy	18% [11]	33% [13]	/	7% [50, 51, 52] 23% [12]	23% [53]

Legend: Act D: Actinomycin D; VP-16: Etoposide; 6-MP: Mercaptopurine; MTX: Methotrexate.

phosphamide, adriamycin, vincristine and then VP-16, procarbazine, bichlorethinylurea. In May 1982 a pregnancy was diagnosed at the 11th week, having started, therefore, while she was taking antiblastic drugs; what is more, during her pregnancy she also took Streptozocine. In spite of this, at the 35th week she delivered a live and vital newborn, without malformations.

Faced by such examples it is clear that up to date we cannot affirm with certainty that an antineoplastic drug is encumbered or otherwise with a determined damaging effect working on the gestational capacity of the patient; we consider, however, that without any presumption of having been definite, we have given some indications that may be useful to those who will probably more and more often have to face this type of problem.

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