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Recent developments in the chemotherapy of female genital cancer

by

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Introduction

The treatment of female genital cancer consists of surgery, radiotherapy or a combination of the two. Both surgery and radiotherapy depend for their success on the complete removal or destruction of all cancer cells. This aim can, therefore, only be achieved if all the cancer cells still remain localised. Unfortunately, it is one of the characteristics of cancers to metastasize; and thus the results of treatment are unsatisfactory. These poor results obtained by treating the female genital cancers by such orthodox methods are clearly seen in Table I and emphasize the need for a better knowledge of chemotherapy. The hope for the future cure of cancer lies in chemotherapy. With the striking exception of the use of methotrexate in choriocarcinoma, however, the results to date of chemotherapy in female genital cancer are extremely disappointing. The drugs as yet available do not have a sufficiently selective biological effect on the cancer cell. But it is more than probable that some drugs will eventually be found which will attack the special metabolism of the cancer cell wherever it may be, leaving unimpaired the normal metabolism of the normal cells.

TABLE I

Results of Surgery and Radiotherapy for Female Genital Cancers

Site of Cancer	Total Number of Cases		Five-year Relative Apparent Recovery Rate (per cent)
Ovary	95	(Kerr and Einstein, 1945)	40
	145	(Pemberton, 1940)	32
	154	(Meigs, 1940)	15.5
Uterine Body	127	(McLennan, 1960)	81
	360	(Gusberg et al, 1960)	54
	368	(Taylor and Becker, 1947)	45
Cervix	3533	(Radiumhemmet, Kottmeier, 1960)	55.6
	3344	(Holt Radium Institute ditto)	41.3
	716	(Royal Marsden Hospital ditto)	37.5
Vulva	65	(Green et al, 1958)	61
	81	(Way, 1960)	58
	102	(Desaive et al, 1950)	27.4

Types of Drugs

These may be summarised in Table II.

TABLE II

Classification of Drugs

I. Polyfunctional alkylating agents also called radiomimetic compounds	Nitrogen mustard Chlorambucil Thio-TEPA Triethylene melamine (TEM) Busulphan (Myleran)
II. Antimetabolites	
(a) folic acid antagonists	Methotrexate Aminopterin
(b) purine antagonists	6-Mercaptopurine 6-Thioguanine
(c) pyrimidine antagonists	5-Fluorouracil (5-FU) 5-Fluorodeoxyuridine (5-FUDR)
(d) glutamine antagonists	Azaserine 6-diazo-5-oxo-L-norleucine (DON)
III. Antibiotics	Actinomycin D Mitomycin C Toyomycin
IV. Miscellaneous agents	Desacethyl methyl colchicine Vincaleukoblastine sulphate (VELBE)
V. Hormones	Oestrogens Androgens Progestogens Corticosteroids

Alkylating agents have the ability to combine with various cell constituents. Destruction of nucleic acid seems to be the key to their success. They are sometimes called radiomimetic agents although their effects and those of irradiation are not precisely similar. Their effects are quicker but short lived whilst those of irradiation are slower but more prolonged. Nitrogen mustard (HN2) may be given intraperitoneally (0.2 mg./kg. repeated once at an interval of 10 to 14 days) in the treatment of malignant ascites or intra-arterially (30 mg.) in the treatment of advanced cases of carcinoma of cervix. Chlorambucil (0.15 mg./kg./day) may be given orally and Thiotepa locally, intraperitoneally or intravenously in the treatment of ovarian carcinoma.

The antimetabolites prevent the formation of DNA by blocking one or more steps in its synthesis. Since the metabolic activity of cancer cells is so much greater than that of normal cells, any such interference can be expected to cause a greater effect on cancer growth than on normal cell growth. Folic acid antagonists such as methotrexate and aminopterin prevent the formation of purines and pyrimidines from simple precursors while the purine antagonists such as 6-Mercaptopurine prevent the synthesis of polynucleotides from the purines and pyrimidines. These drugs

are most widely used in the treatment of choriocarcinoma but are sometimes used in the treatment of advanced cases of carcinoma of cervix and vulva.

Endometrial carcinoma may be treated with progestational agents such as hydroxyprogesterone-N-caproate (500 mg. 2 to 3 times weekly intramuscularly).

Indications

1. Curative chemotherapy—This is possible only in choriocarcinoma which may be treated with methotrexate, 6-Mercaptopurine, actinomycin D and vincaleukoblastine (VEL-BE).

2. Palliative chemotherapy—The chief merit of chemotherapy in all other female genital cancers with drugs that are now available is that it is only a palliative measure. It is usually used when it is apparent that additional surgical or radiation therapy has no further curative or palliative potential or when both of these orthodox methods of treatment are contra-indicated. This may explain why the results of chemotherapy are disappointing. But, on the other hand, it seems unfair to the patient if she is deprived of the orthodox method of treatment when there is still a hope of cure, no matter however remote it may be.

3. Prophylactic chemotherapy—At the time of surgery, cancer cells more often than not disseminate by bloodstreams, by lymphatics, by local dispersion and by intracavity spread. Chemotherapy has been shown to be able to destroy these cells before they have had an opportunity to implant elsewhere, to take root and to flourish. Systemic and or local administration of chemotherapeutic agents should therefore be employed, particularly in the surgical treatment of choriocarcinoma and ovarian carcinoma.

Limitations

From a study of its limitations, one has a better idea as to why chemotherapy is still unsatisfactory and at the same time one can see what are the recent developments and also how further improvements can be made in the future.

1. As it has not been ascertained that the mechanisms of biological activity of normal cells and cancer cells are specifically different, it is not surprising that the former as well as the latter are susceptible to the destructive effects of all chemotherapeutic agents with the exceptions of the hormones, especially the bone marrow, the gastro-intestinal tract and the skin. Leucopaenia, thrombocytopaenia, anaemia, stomatitis, nausea and vomiting, diarrhoea, skin rash and alopecia are commonly encountered. A close watch and an adequate treatment for such side effects are necessary. Some patients are unduly susceptible to these drugs, particularly those who have been recently exposed to radiation, those who are old and generally debilitated, and those with impaired renal function. The following has been carried out to circumvent this disadvantage:—

(*a*) Blood transfusions may be given. Bone marrow is sometimes removed from the patient before chemotherapy is instituted, stored and then reinjected to proliferate normally after the course has been completed.

(*b*) The drugs, *e.g.* nitrogen mustard and methotrexate, may be given by intra-arterial perfusion which cannot be too satisfactorily carried out in the treatment of female genital cancers, or by continuous intra-arterial infusion. The drugs therefore reach the cancer cells in the highest possible concentration. The severity of toxic side-effects will be even further reduced if the specific antidote, when available, *e.g.* Citrovorum Factor or leucovorin or folinic acid in methotrexate therapy, is given at the same time intramuscularly.

(*c*) If it will be shown later that there is a difference between the metabolism of the normal cells and that of the cancer cells, then an ideal drug may be found which will interfere with the latter without affecting the former.

2. Cancer cells seem very capable of adjusting to interfering substances and thus becoming resistant to them. The concomitant use of more than one agent may enhance the destructive ability of these agents without proportionally increasing their toxic effects on the patient. Combined therapy will reduce the rate of, even

if it does not prevent, the development of resistance.

The Use of Methotrexate

The value of methotrexate (which is sometimes given with other drugs such as 6-Mercaptopurine and actinomycin D) in the treatment of choriocarcinoma is undoubted (Chan, 1962); and this is confirmed by figures obtained by Tow (1964) at Kandang Kerbau Hospital, Singapore. (see Table III)

TABLE III

Mortality in (A) Metastatic Choriocarcinoma and (B) Metastatic Choriocarcinoma + Chorioadenoma Destruens in Relation to Treatment

	No. of Cases	Alive	Dead	Mortality (per cent)
A. Metastatic Choriocarcinoma	29	8	21	72
1. Without Chemotherapy	11	1	10	91
2. With Chemotherapy	18	7	11	61
B. Metastatic Choriocarcinoma + Chorioadenoma Destruens	40	18	22	55
1. Without Chemotherapy	12	1	11	91.7
2. With Chemotherapy	28	17	11	39.3

The treatment of choriocarcinoma with methotrexate is now described in detail:—

Methotrexate 5 mg. (2 tablets of 2.5 mg. each) is given 4 times a day orally after blood, renal function and liver function have been assessed until toxic symptoms and signs (the commonest of which are stomatitis and leucopaenia) appear. The average dose is 100 mg. per course. The drug should be repeated after all toxic symptoms and signs have disappeared for a week. The average interval is usually 2 weeks. The number of courses should not be fixed. Methotrexate should be given for another 3 courses after the male toad test has become negative and the pulmonary secondaries (as revealed by X-ray examination of the chest) and secondaries elsewhere in the body—for example, vagina, vulva, skin, gum—have completely disappeared. Methotrexate, 20 mg. in 500 ml. of 5 per cent dextrose, should be given in an intravenous drip just before, during and for 3 to 4 hours after hysterectomy for choriocarcinoma. Intra-arterial infusion has recently been advocated for the treatment of choriocarcinoma in whom the uterus might be conserved (*Bagshawe and Wilde*, 1964).

Muir (1962) treated 9 cases of female genital cancer with methotrexate with disappointing results. Methotrexate has also been used in 5 cases of other female genital cancers: 2 cases of carcinoma of ovary, 2 of carcinoma of vulva and 1 of carcinoma of cervix. The results have been disappointing. The number of cases so treated is so small that no conclusion can be drawn.

Methotrexate given by continuous intra-arterial infusion in advanced cases of carcinoma of cervix, which persists or recurs after radiotherapy and or surgery but which still remains confined to the true pelvis, gives results which are sufficiently encouraging to warrant further trials.

Summary and Conclusions

1. Some of the drugs used in the treatment of female genital cancers are listed, classified and briefly discussed.

2. Curative chemotherapy is possible only in cases of choriocarcinoma. Palliation is all that can be expected in the treatment of other female genital cancers at the present

time. Prophylactic chemotherapy should be more widely used.

3. The main limitations are (a) the production of toxic symptoms which may be very severe or even fatal and (b) the development of resistance by cancer cells to the drug which may be effective to start with. An ideal drug is yet to be found which will destroy the cancer cells without harming the normal ones. Combined chemotherapy will reduce the incidence of development of resistance.

4. The use of methotrexate in choriocarcinoma is then described in some detail whilst its use in other female genital cancers is briefly referred to.

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