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CHEMOTHERAPY FOR OVARIAN CANCER

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From time to time we are asked for details of the chemotherapy regime used at the University Hospital, Kuala Lumpur for ovarian carcinomas. We offer the following paper in response. We find that the easiest way to describe our management is to present a flow chart (Fig 1) and then discuss the various key points along the chart. In this paper we shall concentrate on the regime as applied to the common epithelial tumours: serous, mucinous and endometrioid carcinomas of the ovary.

The initial flow chart regarding surgery is fairly standard among the gynaecologic oncology units, with the exception of one detail. We will not discuss details of our approach to prechemotherapy surgery except to state that we feel it is essential to tailor this very carefully keeping in mind the condition of the patient and the requirements of the subsequent chemotherapy if the chemotherapy is to have its optimal effect, and to point out that the philosophy of surgery for ovarian cancer has been *radically* altered by the advent of chemotherapy.

We continue now to discuss points along Fig 1, starting at point A.

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Point A

In the young, married patient very anxious for a child, the number of reported cases showing successful conception and long term survival following conservative therapy is so large that a case can be made for following these patients without radical surgery, and allowing the patient to conceive.

However we do not encourage *ALL* patients to do so and many factors are taken into account, including the degree of malignancy of the tumour and the wishes of the patient and her husband. Because of the high risk of bilaterality in papilliferous *serous* cystadeno-carcinoma, even if the wedge of the opposite ovary is negative, a more radical approach is recommended. It was demonstrated (Di Saia *et al* 1974) that conservative treatment is best limited to the well differentiated unilateral mucinous and endometrioid tumours whereas the serous and less differentiated carcinomas which are more often bilateral are preferably treated by a more radical operation, including the removal of both adnexae. This has to be kept in mind.

There remain two alternatives: a course of chemotherapy, after which the patient may be allowed to conceive, often without, but in selected cases with a second look operation. Alternatively the patient may be allowed to conceive without prior chemotherapy. While we tend to favour chemotherapy prior to allowing the patient to become pregnant many factors are taken into

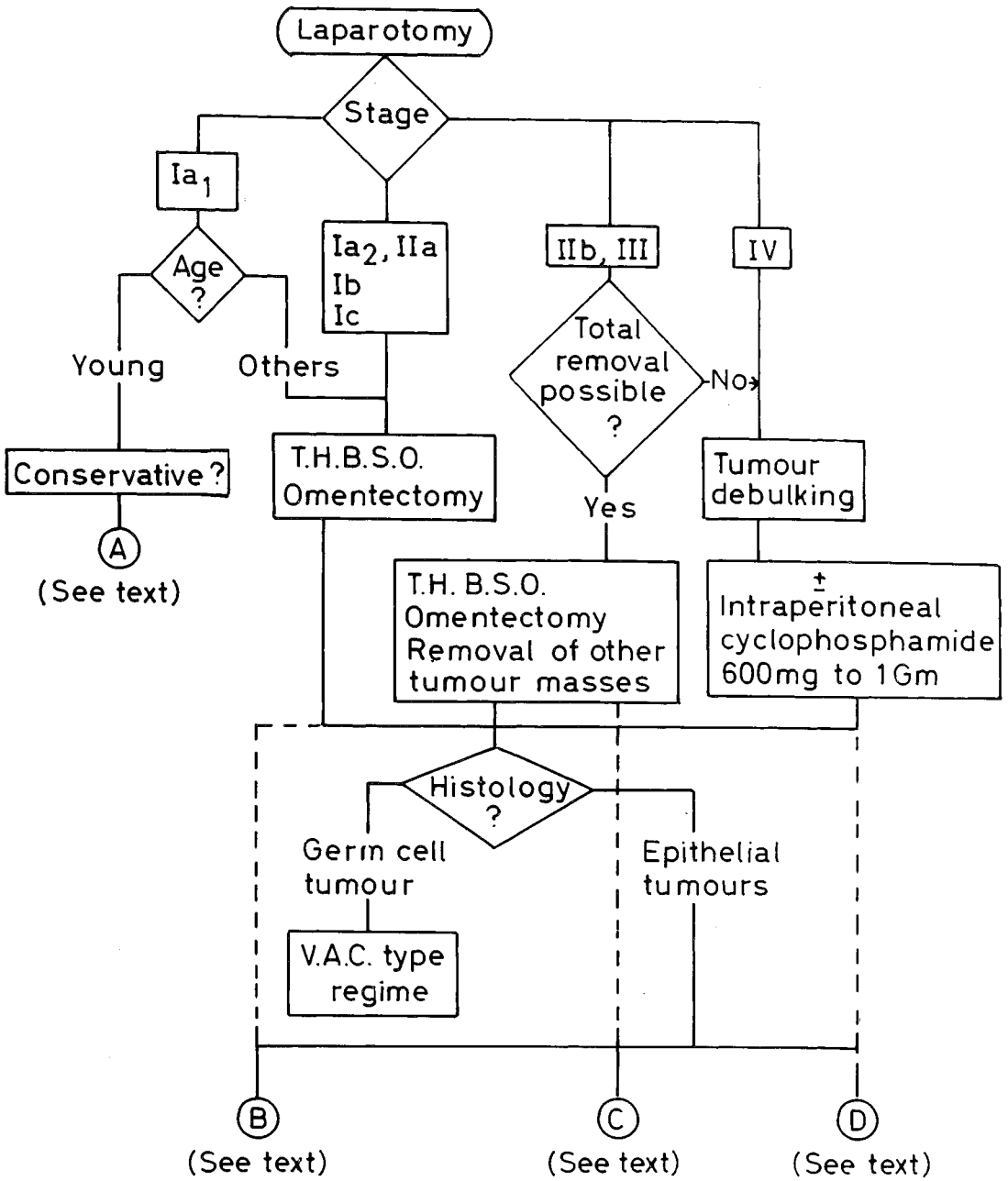

Fig.1 OVARIAN CANCER: FLOW CHART FOR INITIAL SURGERY AND PLANNING CHEMOTHERAPY

account before any of the three possible approaches are taken.

There is a lot of controversy as to the effectiveness of adjuvant chemotherapy in this case. There have been suggestions that adjuvant chemotherapy should be withheld. However we only do so with great caution. The recent results of the American Gynaecologic Oncology Group study quoted by Young (1979) justify our approach in this matter.

Point B

We use a high dose, pulsed single agent cyclophophamide regime which will be described later in this paper, starting on the 10th day postoperatively. Five to seven courses are given, during which standard supervision of toxicity, functional status and surveillance for tumour recurrence are maintained.

Provided these remain satisfactory, and again depending on a number of factors, at the end of either five or seven courses, the patient is put on chlorambucil, 2 to 4 mg. daily, for a minimum of 2 years on a monthly follow-up.

The patients are followed up, after this, initially at 3 monthly intervals for one year at least, then with gradual lengthening frequency. Follow-up continues for life.

Point C

Following surgery for stages IIb and III, where total removal of the tumour has been technically possible the treatment is essentially that at point B of Fig 1, except that we are far more likely to give seven than five courses to such patients and more likely to use 4 mg. of chlorambucil daily than 2 mg.

Obviously great care must be maintained in the search for recurrence. We are in the process of looking at the place of ancillary aids: tumour markers, bone and liver scans, ultrasound and possibly C.T. scanning in the follow-up of these patients. There is an urgent need to look critically and assess carefully the cost-effectiveness of these, particularly in the local context.

The second look operation is important in these patients, as in the next group (see Fig 2), and we feel that generally the minimum time interval between onset of chemotherapy and the second look operation should be approximately one year, at least on our regimes. We have learned the hard way to curb our enthusiasm about the response to chemotherapy. Clinical impression of total regression can be disapointingly shattered if chemotherapy is stopped too early and laparotomy performed.

Point D

Intraperitoneal cyclophosphamide is an anachronism. However we find ourselves reintroducing it. It is important to remember as was stressed recently by Tattersal (1980) that reducing tumour bulk triggers off tumour growth, and chemotherapy to be effective must be given as soon as possible after surgery. One must therefore avoid on the one hand the danger of wound dehiscence, and on the other, a too late start missing out the phase of high mitotic activity and reduced tumour bulk of the early post operative phase.

Members of the team do not all agree on the use of intra-peritoneal cyclophosphamide in the regime: it is well known that cyclophosphamide is only activated in the liver after being absorbed into the system. However it is equally well known that the route of absorption of chemotherapeutic drugs significantly alters the action of the agent on the tumour. Some members of the team have the clinical impression that wound dehiscence has occurred with intravenous cyclophosphamide given on day 2 or 3 postoperatively in our Unit; this has not occurred with intra peritoneal cyclophosphamide and the latter also appears to have reduced the incidence of painful reformation of ascites in the immediate postoperative period. Similar finding have been reported by Ultmann *et al* (1957). Clinical impressions are treacherous things, and we hope to evaluate the problem adequately in the near future.

Cyclophosphamide Courses

The regime itself is described in more detail later and in Fig. 3. At this point we wish to emphasize that the most important parameter deciding continuation of regime is tumour response. So long as tumour response is unequivocally good, the regime is continued, with a decision whether or not to operate and remove tumours (see Laparotomy) being made each time. Response is defined as at least a 50 percent decrease in the production of two measurable tumour diameters (Livingston *et al*, 1976).

Again we are looking critically at how fallacious a clinical impression can be, and at how valuable ancillary methods are in this assessment. Silver marker clips are valuable for radiological assessment, but create havoc if the C.T. scanner is to be used.

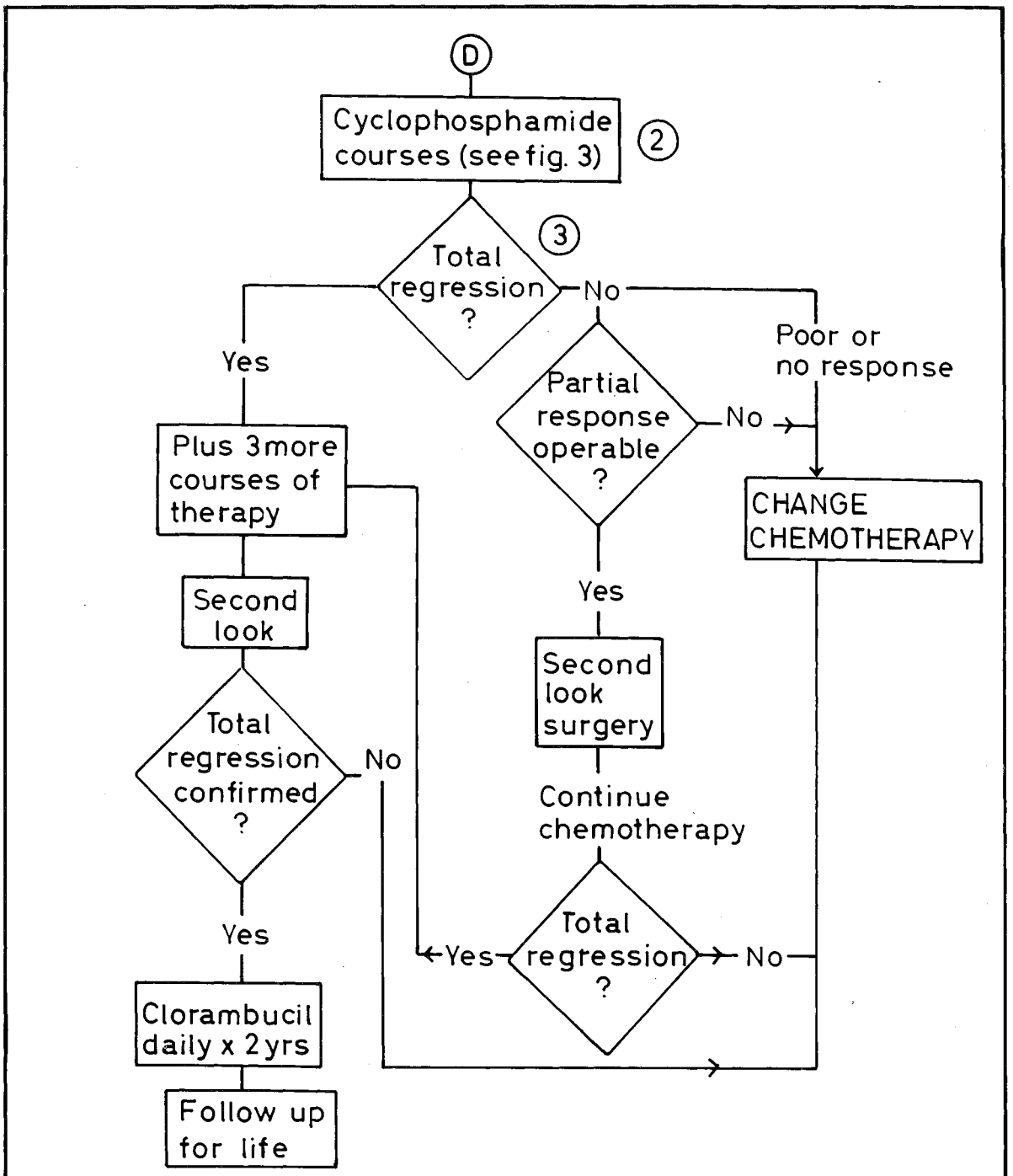

Fig. 2 OVARIAN CANCER STAGE III & IV FLOW CHART OF CHEMOTHERAPY (STARTING FROM POINT (D) IN Fig. 1)

"Total Regression"

When it is considered that the patient has had total regression at least a further three courses of chemotherapy are given before the patient is put on continuous chlorambucil, 4 mg. daily. The timing of the second look has been variable, sometimes prior to, and at others after the patient has been on chlorambucil for some time. This has in the past depended on how many courses of cyclophosphamide the patient has had after "total regression".

Laparotomy

Laparatomy after partial regression has generally been disappointing. Even after the tumour appears more mobile, it has been far more extensive than was originally thought. Both because of this, and because response to chemotherapy is inversely proportional to the amount of tumour left behind, we have tended to be as aggressive at primary surgery as is compatible with smooth post-operative recovery: the aftermath of the operation should not delay the onset of chemotherapy or all the benefits of surgery will be lost by increased new growth initiated by the reduction of tumour mass (Tattersal, 1980).

Multiple Cytotoxic Therapy

Normally response is considered to be present if there is a 50 percent decrease in the product of two measurable tumour diameters (Livingston *et al*, 1976). So long as significant reduction in tumour size occurs during chemotherapy, the course is continued. *At the onset of chemotherapy* this is assessed after two, at most three courses of drug. Subsequently, if there is no regression between any two courses, this is a strong indication for changing to multiple cytotoxic therapy. Waiting too long invites total resistance to chemotherapy.

Currently we use two regimes; a combination regime including cyclophosphamide, methotrexate, Vincristine and 5-FU, and a vincristine, cyclophosphamide, actinomycin-D and adriamycin regime. There are many such regimes and no real superiority of any regime over the other has so far been clearly established. Cis-platinum is now coming into prominence in this field but because of its toxicity, its exact place in the chemotherapy of ovarian carcinomas will have to be carefully worked out and it is very likely that, like adriamycin, it will be most effective in a combination chemotherapy regime.

A multicentric clinical trial of such a combination chemotherapy regime including Cis-platinum is being initiated by the Institute of Radiotherapy, Kuala Lumpur (Dharmalingam, *et al* 1981). It should be very promising and we hope that clinicians throughout the country will give the trial the support and cooperation it deserves.

High dose pulsed cyclophosphamide therapy

This is the regime we use as the basic weapon in our armamentarium and we have now used it as our mainstay for chemotherapy in ovarian carcinoma for over 10 years. It has over these years undergone slight changes and we are beginning to understand its usefulness and its limitations.

The drug is given intravenously in 200 ml. of Dextrose 5% after injecting an antiemetic ½ hour prior to therapy. Initially the blood count is repeated on the 3rd, 12th and 21st day post-chemotherapy. If the patient does not show significant marrow suppression, the 3rd day and the 12th day counts are omitted in subsequent courses. This is a decision made after assessing very carefully the patient's response to her previous courses.

Dosage

The initial dosage is determined by the extent and inherent malignancy of the tumour, the age and general condition of the patient, prior therapy, and the presence of ascites. The prime principle, except in stage Ia tumours, is to achieve the maximum dosage that the patient will tolerate. The very old patient and the patient with previous radiotherapy respond with prolonged and severe leukopenia. Dosage has to be determined with great care in these patients. The patient with ascites also does so, probably because the drug pools in the fluid and therefore acts longer than usual on the system. Using the normal dose of drug can therefore result in fatal leukopenia. We subtract by weight the estimated amount of ascitic fluid, and start with the lowest (30 mg/kg) concentration in these cases. Others have used concurrent peritoneal dialysis to overcome this problem (Wallach *et al*, 1976). After careful review of the previous response to chemotherapy the dosage is set up. As the nadir of the wbc count occurs at around the 12th to 14th day, dose increases are only allowed if the *previous* 12th to 14th day white count is available.

A final factor in determining dosage is the white cell count immediately prior to therapy. *We do not have a fixed level at which we consider it safe to start therapy.*

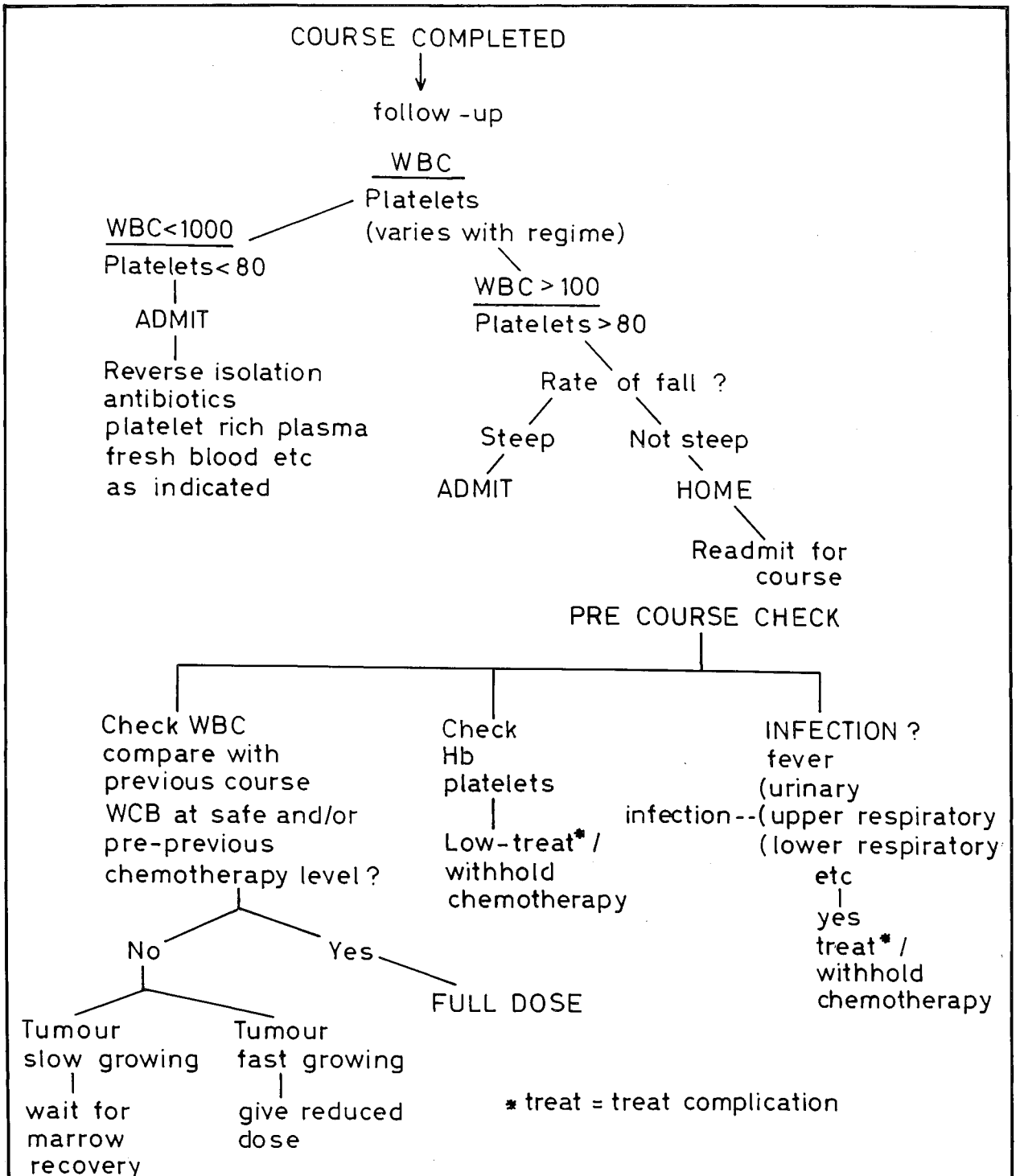

Fig. 3 FLOW CHART FOR CHEMOTHERAPY REGIMES

The patient with an initial white cell count of 5000/mm^3 whose 12th day count is 1000/mm^3 and is seen on the 21st day post chemotherapy with a count of 3000/mm^3 will almost certainly have a potentially lethal leucopenia if she is given the same dose of drug as in the previous course. Fixed protocols for altering drug dosage in M.D. Anderson Hospital trials is given by Livingston *et al* (1976).

There are two choices open at this point: either to lower the dose of the drug, or to delay treatment until a more satisfactory white cell count is obtained. The decision as to which course to take is based on a complexity of factors including growth rate of tumour, tumour response to drug, and patient's rate of marrow recovery in previous courses. No simple answer can be given.

To summarise — at the start of each course, we ask ourselves three questions: how did the patient behave with respect to the drug? How did the tumour behave? How much, if any, drug do we give now? In other words, we look at toxicity, at infection, which is a contraindication for cytotoxic therapy, and at response, not only of the tumour, but of the patient as well. It can be necessary to sit with a patient for over an hour to convince her that tumour response is so good that it is worth her while to continue accepting the side effects of the regime.

Our preliminary results were presented at the 6th Asian Congress of Obstetrics and Gynaecology in Kuala Lumpur in 1974. We are in the process of redrawing our Oncology Register taking into account the difficulties and limitations of the previous years. But the results that can be expected with this kind of cyclophosphamide regime are in the order of 88 percent initial objective response as reported by Geisler (1976).

CONCLUSION

An outline of the management for the common i.e. epithelial cancers of the ovary is presented, and we have discussed in some detail those areas in the management where either problems commonly arise, or where the way of making decisions significantly affects the quality of care, and the results.

We have found that as small a change as moving from four to three weeks between courses has apparently made a significant reduction in the number of women waiting agonising death with distended abdomens. Shorter time intervals have been recommended.

There are those who will object that the regime as described is too complicated, and that its multifactorial nature makes it difficult to reproduce. Unfortunately, we feel it is impossible to simplify this without a drop in the quality of care extended to our patients. The ultimate aim is not to produce a simple regime but to cure patients.

We feel it is important to remember also that where we cannot cure the patient, we must make her as comfortable as possible. This is, we feel, a major area in the management of cancer patients which has been generally neglected (by us as well) and to which it is important that a lot of attention should be given as soon as possible.

It goes without saying that no unit can adequately treat cancer patients if it does not consider the social and psychological impact of the disease on the patient.

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