Ovarian cancer clinical survey

A. W. HARCUS
M.B., CH.B., D.OBST., R.C.O.G.

Schering Chemicals Limited, Burgess Hill, Sussex

NEWTON & White (personal communication) reported on a series of twenty cases of advanced ovarian cancer treated with Primolut Depot (17-alpha-hydroxy-progesterone caproate), and although their results were encouraging, it was disappointing that the beneficial effects of this regime, such as improvement in the quality of life, regression of lymph nodes and decrease in tumour size, were offset by discomfort caused by the volume of the injection—up to 4 ml three times a week.

A new progestagen, Depostat (gestranol hexanoate, SH 582), with a progestagenic activity twenty to twenty-five times that of Primolut Depot, seemed an excellent alternative and was supplied to several interested clinicians for assessment. By the end of 1970 about thirty-four cases had been studied and, although the observations appeared to support the previous findings, it was obvious that investigations would have to be made on a much larger scale if the results were to have statistical significance and not remain as purely personal impressions. The need for this was emphasized by Barr at the 19th British Congress of Obstetrics and Gynaecology in Dublin (1971) when he described his series of twenty patients and called for a co-ordinated countrywide investigation.

With the help of a group of gynaecologists and radiotherapists, therefore, a protocol has been designed for a multicentre survey, the object of which is to study the effect of administering a progestagen and a cytostatic agent, either alone or in combination, on the disease-free interval, survival time and quality of life in patients with a histological diagnosis of ovarian cancer.

There may be ethical objections to random allocation of patients with cancer into control groups, but a generally acceptable compromise has been reached. It is customary for patients with early disease, from whom all known tumour tissue has been removed, to be sent home without additional treatment other than perhaps radiotherapy until such time as they present with evidence of recurrence. It has been suggested that this disease-free interval may be prolonged by progestagen therapy and, as it would not be unethical to randomly allocate half of these patients to a

treatment group, a comparison can be made of the times from initial diagnosis to recurrence.

When, on the other hand, the patient returns with recurrence or presents initially with more advanced disease, it is unlikely, although not impossible, that the clinician would be prepared to withhold additional therapy. As there seems to be no clearly defined treatment of choice for these patients at present, it is justifiable for them to be randomly allocated into one of the following three treatment groups: progestagen alone, cytotoxic alone, or a combination of cytotoxic and progestagen, thus enabling a comparison of the quality of life and survival time to be made.

What is meant by the term 'quality of life' and how can it be assessed? Many existing methods attempt to measure the ability of a patient to perform certain routine tasks, such as climbing stairs, dressing and coping with household chores. These activities, which may be greatly influenced by the patient's social status and environment, could be misleading and it has been agreed that six factors should be considered for the purposes of this study:

- (a) the presence or absence of pain;
- (b) the presence or absence of appetite, nausea or vomiting;
- (c) activity, rated as normal, reduced or bed-ridden;
- (d) weight;
- (e) necessity for paracentesis;
- (f) need for additional drug therapy such as analgesics, which may prove to be a very useful indication of the patient's condition.

It is anticipated that factors (b) and (c) will be progressive and provide a crude qualitative measure.

If a number of patients appear to respond to treatment, predictive factors must be searched for and identified if possible. The information required for this can be obtained in one of two ways; either retrospectively by going through patients' case-notes, trusting that relevant data have been recorded, or prospectively by the collection of information at the time of consultation and examination. The latter

method has been selected in the belief that it will prove simpler and more reliable in the long run.

Information, once collected, has to be recorded and stored until required for analysis. Special report forms have had to be prepared for this purpose with two criteria in mind. The time required by the clinician must be kept to a minimum and the data must be presented to the statistician in a usable form. A multiple choice format has, therefore, been adopted as ticking is quicker than writing and a large number of questions may require only a single tick.

The following basic information is being collected:

- details for identification of patient;
- general history;
- gynaecological and obstetric history;
- present condition;
- clinical findings;
- operative findings;
- histological findings.

The procedure for random allocation of patients into groups could be cumbersome and cause unnecessary delays in commencing therapy if reference to the co-ordinating centre was required for each individual. In order to streamline the procedure, two randomization envelopes are attached to each set of coded registration forms. The investigator is asked if, in his opinion, it would be ethical for the patient to receive no further treatment at this stage and, if so, he is then instructed to open the envelope marked 'Randomization 1' which contains a card allocating her into the 'no treatment' or 'treatment with progestagen' group. If, on the other hand, it would not be ethical for the patient to receive no further treatment, the envelope marked 'Randomization 2' is to be opened and she will be allocated into one of the three possible treatment groups.

The study has been designed to interfere as little

as possible with the practice of individual clinicians and it has been possible to arrange for the collection of much useful data while leaving many of the decisions to the patient's own medical adviser as, for example, the option to refer for radiotherapy, the choice of cytotoxic drug, the selection of first or second level randomization and, of course, the freedom to change the treatment should this be considered necessary. It may be argued that freedom to change the treatment will defeat the purpose of random allocation, but it is presumed that such a change will only be made when the existing form of therapy has failed to control the disease and can, therefore, be regarded as a measurable end-point.

Overall co-ordination of this study, by which is meant distribution and collection of report forms, checking that they have been completed properly and converting the information to cards for computer storage, is the responsibility of Miss J. K. Nesbitt at the Department of Medical Statistics, Institute of Clinical Science, Grosvenor Road, Belfast, and there are local co-ordinators in Dublin, Guildford and Newcastle.

So far, the ovarian cancer clinical survey has been well received and the response has been most encouraging. Gynaecologists and radiotherapists from many centres have pledged their support and there has been considerable interest from a number of workers overseas. Enquiries have been received from Austria, Australia, Belgium, France, Italy, Poland, South Africa, Switzerland and the United States and it is hoped that co-operation with some of these countries will be possible.

In addition to the primary objectives of the survey, it seems that the stimulation of inter-regional co-operation may lead to secondary studies and it has already been possible to arrange for the exchange of tumour tissue between research centres. Feedback of information must not be overlooked in a survey such as this and a regular newsletter will be sent to anyone who has expressed interest.