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Treatment of Early Ovarian Cancer

THE PAPER by Chiara and coworkers (p. 1211) is a good example of a cooperative multicentre effort to study a relatively rare gynaecological tumour. The basic problem of early ovarian cancer is the lack of referral to cancer centres where clinical research programmes are being conducted. This is quite understandable from a clinical point of view as the diagnosis of early ovarian cancer is often made at the time of laparotomy for other reasons and therefore unexpected. From the research point of view it is dramatic. It necessitates to undertake multicentre trials with many different institutions and with all the difficulties and problems to get various policies and clinical circumstances into the same direction. The Italian paper shows some of these difficulties.

The studied population combined patients treated primarily in one of the GONO institutions with women who were referred after prior surgery elsewhere. The latter category, in which surgical staging was not performed according to preset criteria, formed 17% of the total group. Surgery in these non-GONO hospitals was considered inadequate and these patients were restaged at second-look surgery after chemotherapy. A total of 15 patients underwent incomplete initial surgery. The indication for second-look surgery was made at the discretion of the responsible gynaecologist. A total of 40 second-look procedures was performed, but only in 10 of the 15 patients with an inadequate initial operation. This is confusing. Only 10 of 15 patients with inadequate staging underwent restaging later and 30 of the remaining 69 patients had a second-look procedure on the basis of personal preference of the gynaecologist in charge. These figures cast some shadow over the value of the relapse-free survival reported in the study.

The criteria for adequate staging in the study suggest that a difficult compromise was reached between participating institutes. It is not clear why multiple random biopsy samples were not taken from the paracolic gutters a side at high risk for implantation metastasis [1]. Furthermore, retroperitoneal lymph node sampling was only performed in the case of clinically suspicious nodes. The Miami group has, already some time ago, demonstrated that the diameter of metastatic lymph nodes for the greater part overlap that of non-metastatic lymph nodes in women with gynaecological cancer [2]. Recently it was shown again in a large GOG study of patients with early ovarian cancer that the clinical impression of the lymph node status (negative or positive) is an unacceptably poor discriminative tool [3].

It remains difficult to define staging criteria in ovarian cancer that are both scientifically sound and also feasible and acceptable in a multicentre study. The EORTC gynaecology group has debated the various staging steps extensively and has formulated the criteria that an optimal staging procedure should fulfill [1].

The composition of the study population in the Italian study also deserves some attention. A total of 87 patients with stage I and II ovarian cancer were treated. 28 of these patients had a stage IIb or IIc disease that cannot be reckoned among the early stages of ovarian cancer. In virtually all series, stages IIb and IIc are considered the same and treated identically as compared to advanced stages III and IV. 48 of the remaining 59 patients were in stage Ic and 7 in IIa. This leaves only 4 patients with Ia and Ib disease, definitely too small a number to permit any conclusion on tumour behaviour of these stages. The relatively large number of patients with Ic disease results from the new FIGO classification in which former Ia2 and Ib2 tumours are now defined as stage Ic. Furthermore, the new FIGO classification Ic does not distinguish between surgical rupture at operation, tumour rupture before surgery, malignant peritoneal washings or malignant ascites. It is therewith, a compilation of patients with different prognostic factors, hampering valid conclusions on the biological behaviour of early ovarian cancer.

So, what does the study of Chiara *et al.* teach us in the end? It shows that six courses of cisplatin-containing combinations, is a feasible treatment with acceptable morbidity in patients with minimal or non-residual ovarian cancer at the time of chemotherapy. The study confirms the findings of others that tumour

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grade is important in ovarian cancer and it demonstrates the pitfalls and difficulties of conducting a multicentre trial in early ovarian cancer. One of the things it does not tell us is whether adjuvant chemotherapy is worthwhile in early ovarian cancer.

The clinical significance of adjuvant chemotherapy in early ovarian cancer is still unanswered and is one of the major issues of the treatment of this disease. This white spot is undoubtedly due to the incomparability of data from different trials. In some studies borderline tumours have not been excluded and due to differences in the extensiveness of surgical staging, stage I does not mean the same thing around the world. Furthermore, the consistency of histological grading is even more wishful [4].

By definition, early stage ovarian carcinoma is macroscopically localised to the internal genitals within the small pelvis. Nevertheless 30–50% of patients with early ovarian cancer relapsed after seemingly adequate treatment for localised disease [5]. The 5-year survival rate after surgery often followed by some other form of treatment in large cumulative series with a long duration of follow-up amounts to 70% in stage Ia, 64% in stage Ib, 50% in stage Ic and 52% in stage IIa [6, 7]. This relatively poor prognosis has led to a variety of studies testing different adjuvant treatments after surgery during the last decade [8]. The majority of these studies suffered from a number of shortcomings such as the omission of a therapy-free arm in the "high risk" early stages [9, 10], non-exclusion borderline tumours [11] and an incomplete surgical staging [12] as judged by the present standards [13].

It has been shown that surgery alone can be considered as a sufficient treatment in well-differentiated stage Ia and Ib disease, be it that meticulous surgical staging should be performed [4]. The only way to proof the possible benefit of adjuvant treatment in the remaining patients (grade II/III, stage Ia/Ib: all stages Ic/IIa) would be by means of a prospective randomised trial with a therapy-free arm. It seems like a historical omission that such a trial has not been undertaken a long time ago. But then such a situation is not completely rare in medicine. The same can be said of the generally praised concept of cytoreductive surgery in advanced ovarian cancer. It was introduced, vigorously recommended, widely accepted and commonly practised [14]. Now, 10 years later, the knowledge of prognostic factors in advanced ovarian cancer has greatly expanded, permitting a new prospective on biological tumour behaviour. But now, it may be too late to ever answer the question whether the benefits of successful cytoreduction are related to surgical skill or merely to favourable tumour characteristics [15]. It seems an appropriate time to include a treatment-free arm in randomised clinical trials on the role of adjuvant treatment in early stage ovarian cancer. Surgical staging of the disease is much more clearly defined than before and based upon modern knowledge of the metastatic spread of ovarian cancer [16]. This makes the possibility of unappreciated advanced disease smaller and enhances the success rate of treatment modalities suitable for localised disease, such as surgery. Furthermore, the accuracy of follow-up has also significantly increased by the use of tumour markers as CA-125. For those who would still be reluctant to include their patients in a therapy-free arm it is noteworthy to mention the work of Guthrie and coworkers [17]. They did a meta-analysis of a large collected series of patients from European trials and could demonstrate a significantly better survival in patients with early ovarian cancer who received no adjuvant treatment as compared to those who had either radiotherapy or chemotherapy or both following surgery [17]. In a recent prospective randomised trial, Italian investigators found no significant difference in survival after 3 years between patients with stage Ia/Ib, grade II/III ovarian cancer who received no adjuvant treatment after surgery and those who did (6 cycles cisplatin, 50 mg/m^2) [18].

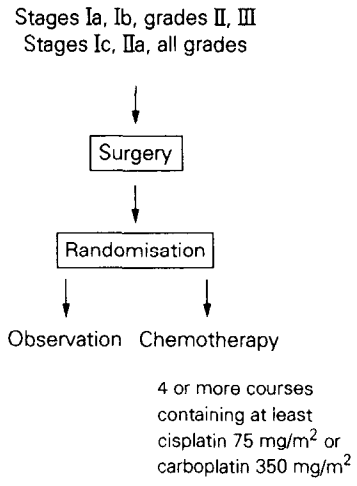

Fig. 1. Study design of the EORTC ACTION trial in early ovarian cancer.

In 1990 the EORTC ACTION protocol in early ovarian cancer was started. The study design of this "adjuvant clinical trial of ovarian cancer" is illustrated in Fig. 1. European guidelines of staging in ovarian cancer (EGSOG) are used as an entry criterion and recommendations for tumour morphology grading are given. The trial has been deliberately kept simple to permit a wide participation from all over Europe. Patients are randomised into two groups: adjuvant chemotherapy versus no adjuvant treatment. The kind of adjuvant therapy is left to the discretion of the participating institution as long as it contains at least four courses of a platinum derivative. Furthermore, every institution has the choice to include stage Ic in the study or not. A large number of evaluable patients are needed to reach statistically sound conclusions. Therefore the ACTION trial is open to centres outside the EORTC gynaecology group as well. Interest and participation from all over Europe has been noted.

Interestingly an independent initiative by the Medical Research Council has resulted in a similar trial in the UK. This trial, called ICONS (International Collaborative Ovarian Neoplasm Studies), addresses early as well as advanced ovarian cancer. In early ovarian cancer, adjuvant chemotherapy (at the discretion of the responsible gynaecologist) is compared to no treatment following surgery.

In the years to come the results of the ACTION and ICONS trials will be compared and, wherever possible, combined in order to finally answer the question whether adjuvant chemotherapy in early ovarian cancer should be considered as necessary treatment or merely overkill.

J.B. Trimbos
Department of Gynecology
University Hospital
Rijnsburgerweg 10
2333 AA Leiden
The Netherlands

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Phase II Studies: Wrong Doses, Wrong Patients?

IN DEFIANCE of recent trends in clinical research, phase II testing of new anticancer agents is still carried out in uncontrolled studies using small numbers of patients. Are current procedures adequate to ensure that the goals of identifying active agents rapidly, accurately and safely are met?

In phase II trials, a defined dose and schedule are tested in specific tumour types. Success or failure at this stage will determine the subsequent future of the drug. In spite of recent advances in our understanding of the underlying genetic processes which cause cancer, the majority of new anticancer drugs currently in development are antiproliferative agents with a relatively small therapeutic index. It is usually necessary to administer such drugs at the maximum tolerated dose (MTD) in order to achieve optimal antitumour activity. Hence, a successful phase II study is critically dependent on the use of an adequate dose and appropriate schedule. Success also depends on careful patient selection.

If known, a knowledge of the mechanism of action of a drug will help to guide the choice of schedule and a good phase I study will help to ensure that an adequate dose is chosen for phase II trial. In the traditional phase I study 3 patients are entered per dose level, dose escalations are performed using a "modified Fibonacci" scheme and the MTD, or "highest safety tolerable dose", is defined [1]. This is generally regarded as that dose causing grade III myelosuppression, diarrhoea, or mucositis or grade II-III renal, hepatic pulmonary, cardiac or neurological toxicity. The dose chosen for phase II study is then usually one dose level below the MTD. If this scheme is used unimaginatively it is possible to recommend a dose for phase II study which is 30–40% lower than the MTD and which has only been administered to 3 patients! Pharmacokinetics can be used to expedite dose escalation and also to correlate drug concentrations at the MTD with those known to be effective against experimental tumours [2, 3]. If such concentrations cannot be achieved in man owing to toxicity then further evaluation is likely to be fruitless. Before determining the phase II dose it is advisable to treat a larger group of patients at just below the MTD in order to determine the degree of interpatient variation in toxicity and pharmacokinetics. The sort of patients available for phase I trials may not tolerate chemotherapy well, especially if they are heavily pretreated, and one may need to consider the option of defining separate MTDs for non-previously treated and heavily pretreated patients. Another approach to the problem of correct dosage is to recommend dose escalation if a predetermined level of toxicity is not observed after the first course. Conversely, dose reductions will, of course, be allowed if toxicity is excessive.

If failure to choose the right dose and schedule can result in a falsely negative phase II study, what about the choice of patients? It is known that previous exposure to cytotoxic drugs and radiotherapy may lead to the induction of drug resistance, in some case due to increased expression of P-glycoprotein or via an increase in glutathione S-transferase activity [4, 5]. Because of the impact of acquired resistance on response rates it would be ideal if one could test new drugs in previously untreated patients. However, there are practical and ethical problems with this approach in disease types where conventional treatment is reasonably effective, at least in terms of short-term symptom control.

For example, metastatic breast cancer is generally regarded as incurable, hence the administration of a new drug prior

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