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Chemotherapy for Ovarian Cancer

S.B. Kaye

INTRODUCTION

POPULATION STUDIES have indicated that over the past 15–20 years, the overall mortality for ovarian cancer has improved, particularly for younger patients [1]. Since earlier diagnosis of the disease is most unlikely to have occurred, it is likely that these changes reflect improvements in management. Whether this involves changes in surgical practice or improvements in chemotherapy, e.g. the introduction of cisplatin, requires further study. Nevertheless, ovarian cancer remains the most lethal of the gynaecological cancers, and it represents a continuing challenge to both medical and gynaecological oncologists. Some of the main questions in treatment in 1993 are discussed in this review, the purpose of which is to examine these issues and offer some comments which might serve as a basis for continuing clinical research in these areas.

WHICH PATIENTS WITH EARLY DISEASE SHOULD RECEIVE CHEMOTHERAPY?

Some 20% of cases of ovarian cancer, after careful surgical staging, fall into the category of FIGO stage I, i.e. growth limited to one or both ovaries. A continuing dilemma for oncologists is whether or not such patients should receive additional treatment, the aim being to eradicate any microscopic metastatic disease.

Features which are frequently used to help in decisions over management include the histological grade of the tumour, the presence of tumour on the external surface, presence of an intact ovarian capsule, and the presence of adhesions within the pelvis, or of ascites containing malignant cells or positive peritoneal washings.

Although stage I patients with one or more of these adverse prognostic factors are often treated with chemotherapy (or intraperitoneal ^{32}P [2]), its use in the "adjuvant" setting has not yet been shown in controlled randomised trials to be of value.

A wide range of clinical practice can in fact be seen, and variations in surgical practice, particularly staging procedures, can add to the problem. Some investigators would routinely treat stage I patients with adverse prognostic features with cisplatin/carboplatin-containing chemotherapy, while others would consider no initial treatment as a valid option for patients with stage I and even completely resected stage III disease. Data recently presented from a large randomised trial which included the use of cisplatin for stages Ia and b disease showed no difference in survival compared with no treatment, although there was a difference in 5-year disease-free survival (76 vs. 58%, $P < 0.05$) [3]. Clearly, longer follow-up is required, and in addition, much larger randomised trials, such as that initiated by the MRC Gynaecological Cancer Subgroup (ICON-I) [4] are needed, in which a policy of observation is compared with initial cisplatin- or carboplatin-containing chemotherapy for patients whose disease has been completely resected.

In the future, analysis of tumour ploidy [5] and levels of expression of mutant p53 protein [6] may significantly help in decision-making in stage I disease.

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CARBOPLATIN VS. CISPLATIN, ARE THEY THE SAME?

Perhaps the most common concern for clinicians treating advanced ovarian cancer relates to the issue of carboplatin instead of cisplatin. The question to be answered is: when used in combination schedules, are the two drugs therapeutically equivalent in terms of anti-tumour activity? Clearly if they are, carboplatin would be the preferred choice, since the drug is generally better tolerated by most patients. Despite the introduction of new antiemetics [7] and the promise of new neuroprotective agents [8] the gastrointestinal and neurological toxicities of cisplatin remain considerable disadvantages. Nevertheless, it would be inappropriate to propose that its use should be discontinued until it is clear that carboplatin provides just as effective tumour control in all circumstances.

The problem with carboplatin is that it causes rather more myelosuppression particularly thrombocytopenia than cisplatin, and this has led to a variety of difficulties in interpreting the results of published data.

Firstly, it is clear that when used in combination with other agents such as cyclophosphamide, adjustments in dose of carboplatin are required, and this is generally not the case with cisplatin. How much does this matter? The answer is not clear but this may not be a trivial issue. We now know that for cisplatin, a clear dose–response effect is seen, at least over the dose range of 50–100 mg/m^2. This was demonstrated in a recent study from Scotland, in which 191 patients with advanced ovarian cancer were randomised to receive six three weekly cycles of cyclophosphamide 750 mg/m^2 with either 50 or 100 mg/m^2 of cisplatin. The trial was closed when a highly significant survival difference, in favour of the higher dose arm (P = 0.0008) was noted [9].

Does such a dose–response relationship exist for carboplatin? In the absence of formal randomised trials comparing different dose levels, the answer is probably yes, but it remains unknown as to whether reductions in the range of 25% of carboplatin dose when used in combination with other agents will compromise its efficacy.

A further problem with the use of carboplatin relates to the fact that apparently wide interpatient variability exists in drug handling. This means that in contrast to cisplatin, for which doses are generally presented on a mg/m^2 basis, the individual dose recommendations for carboplatin have given rise to considerable confusion. Some centres will routinely prescribe carboplatin at doses of 400 mg/m^2, while others will describe the use of a calculated dose using an equation such as the Calvert formula, based on renal function [10]. This does take account of variations in drug clearance, but even so it is clear that a substantial number of patients could receive further dose escalations, as judged by the absence of myelosuppression on day 21 of a 4-week treatment cycle. The importance of this has recently been demonstrated in a study in which a significantly poorer outcome was noted for patients treated with carboplatin who did not demonstrate significant myelosuppression compared to those who did [11].

Notwithstanding these issues, a number of comparisons have been made between carboplatin and cisplatin, either used alone or in combination, for the treatment of advanced ovarian cancer. Two problems exist in the interpretation of these data. The first is that the trials involved are generally too small to define a difference which could prove to be clinically significant. For this reason, overview (meta)-analysis methodology is useful, and such an analysis has recently been published. This has shown that over the first 3–4 years, there appears to be no significant survival difference in trials in which the two drugs have been compared, either as single agents or in combination [12]. However, minor differences may begin to emerge after 5 years of follow-up, and further long-term follow-up is therefore necessary.

The second problem, not addressed by the overview analysis, is that of cross-over. In most trials, patients who eventually relapse after initial treatment with carboplatin (obviously the majority) may receive subsequent treatment with cisplatin. As is well known, the response rate in this situation depends on the time interval since the initial chemotherapy, but it may be substantial, and the impact of this on overall survival could be considerable. In trials comparing carboplatin with cisplatin, such a cross-over is a major complication to the interpretation of survival comparisons, and it is widely accepted that survival rather than response comparisons are the most appropriate means of assessing therapeutic differences. Interestingly, a trial conducted in France has recently been reported, in which carboplatin in combination was directly compared to cisplatin in combination, and cross-over was not allowed, i.e. patients relapsing on the carboplatin arm were retreated with carboplatin only [13]. This trial showed a significant survival advantage for the cisplatin-containing arm, in contrast to other studies in which cross-over was presumably allowed, but the number of patients is small, and the results should be interpreted with caution.

In the author's view, therefore, the weight of evidence at present does not allow for the routine substitution of cisplatin by carboplatin. Clearly, carboplatin is preferred if there is a question about tolerance to chemotherapy. However, cisplatin in combination with cyclophosphamide is still a reasonable choice of therapy for many patients. In this situation the dose of cisplatin should be at least 75 mg/m^2. A recently completed study in Scotland has shown a clear survival advantage when the dose of cisplatin of 100 mg/m^2 is compared with only 50 mg/m^2, but as expected the higher dose leads to more toxicity, and for routine usage outside clinical trials, a dose of 75 mg/m^2 of cisplatin in combination with cyclophosphamide is a reasonable compromise [9].

WHAT ABOUT OTHER DRUGS?

What role do other agents play in the management of advanced ovarian cancer? It is well known that alkylating agents have significant single-agent activity in this disease, and cyclophosphamide is the one most frequently used. Randomised trials have confirmed that at least in terms of response, combination schedules including cyclophosphamide and cisplatin are superior to single-agent cisplatin therapy [14]. Other alkylating agents which are available for use in occasional circumstances include chlorambucil, thiotepa and treosulphan. All of these drugs may be given orally, do not generally cause alopecia, and may occasionally be appropriate for patients for whom intravenous treatment is considered inappropriate.

The exact role of anthracyclines in the management of ovarian cancer continues to excite controversy. Once again this is an issue in which small trials can give conflicting results. However, a recent overview analysis does suggest that a tangible benefit, in terms of survival, can be expected if anthracyclines are used in initial treatment combinations [15]. The problem, of course, is that in using anthracyclines, doses of the other agents in the combination may require to be reduced, and this may compromise its overall efficacy. For instance, is there any

difference in efficacy between a combination including cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and cisplatin 50 mg/m^2, compared to cyclophosphamide 750 mg/m^2 and cisplatin 75 mg/m^2? It seems likely that the answer is no, in which case a decision to include the anthracycline may relate to issues of comparative toxicity, and for many women alopecia is the side-effect which causes the most concern.

In terms of other agents, the most intriguing data are those relating to the new drug, taxol. Although its preclinical assessment took place several years ago, it was only in 1989 that the drug's potential in ovarian cancer became apparent [16]. Its activity in patients whose disease was clearly refractory to cisplatin was first noted in phase I trials, and confirmed in three separate phase II studies, the data from which have been reviewed externally (B. Winograd, personal communication). The overall response rate from these three phase II trials for taxol among 118 previously treated patients with ovarian cancer was 37% (34 responses). A total of 9 of 51 patients (18%) whose disease had clearly progressed during prior cisplatin therapy responded to subsequent taxol treatment, while 4 of 17 (24%) patients with "no change" on previous cisplatin responded to taxol. A total of 18 of 46 (39%) patients whose disease relapsed after completing cisplatin responded to subsequent taxol, with no clear trend in response rates with longer disease-free intervals.

Taxol is a new agent with considerable promise, but it clearly also presents problems in terms of side-effects as well as in terms of drug supply. Substantial myelosuppression, alopecia, neurotoxicity and occasional allergic reactions are the major manifestations of toxicity. Moreover, the agent is derived from the bark of the Pacific yew tree, of which there is a finite supply. Recent intensive efforts have been made in order to develop a method for the partial chemical synthesis of the compound, and early results are apparently promising. Current efforts are directed towards elucidating the precise role of taxol as part of first-line therapy in ovarian cancer, particularly in combination with cisplatin.

In addition, a taxol analogue, taxotere, derived through a semi-synthetic process from the leaves of the European yew tree *Taxas baccata* is also undergoing clinical trials [17]. This agent possesses very similar properties to the parent compound *in vitro*, with an evident increase in potency. Phase I trials with taxotere indicated that myelosuppression was dose limiting, and antitumour activity in ovarian cancer was seen (Kaye, personal communication). Phase II trials with taxotere are ongoing, and a key question will be to determine whether there is any difference in the therapeutic index of this agent compared to taxol.

WHAT IS THE OPTIMAL DURATION OF TREATMENT?

The number of courses of chemotherapy given to patients with advanced ovarian cancer varies considerably, and the impact of this may have been underestimated in previous analyses, since this provides a direct measure of the total dose of drug delivery. The importance of delivering an adequate total dose is highlighted by comparison of two similar trials recently published. The first, conducted by the Gynecologic Oncology Group (GOG) in the U.S.A. with 490 patients with advanced ovarian cancer randomised the patients to receive either cyclophosphamide 500 mg/m^2 and cisplatin 50 mg/m^2 for a total of eight courses, or else cyclophosphamide 1 g/m^2 and cisplatin 100 mg/m^2 for a total of only four courses. Thus the dose intensity on a mg/m^2/week basis, was essentially doubled in the high-dose arm, but the duration was halved, so that the total dose of cisplatin (400 mg/m^2) was the same in both arms. No significant difference in overall treatment outcome was noted [18].

On the other hand, in the trial in Scotland mentioned above, in which 190 patients were randomised to receive cyclosphosphamide 750 mg/m^2 and cisplatin 50 mg/m^2 (low dose) or 100 mg/m^2 (high dose), treatment in both arms continued for six cycles. Thus, the total planned dose of cisplatin in each arm was 300 and 600 mg, respectively. The total dose actually received, for reasons of toxicity, was actually 300 and 500 mg, respectively. A highly significant survival advantage was seen for the high-dose arm, albeit at the cost of significantly greater toxicity, in the form of neurotoxicity, nausea and vomiting, alopecia and myelosuppression [9].

This comparison does demonstrate that an important component determining treatment efficacy is the total dose of the most active agent involved (cisplatin or carboplatin). One might be tempted to conclude that the total dose should, in general, be in the region of 400–500 mg. The problem is that at levels above this, significant numbers of patients will develop troublesome neurotoxicity, and better methods to alleviate this are clearly required. Here carboplatin has a clear advantage, and the task for clinical investigators now is to define an optimal total dose of carboplatin, and then translate this into a recommended number of courses.

In practical terms, and for most patients, six courses of treatment is a number which is broadly acceptable, and the dose per course should be calculated on that basis. Longer courses of chemotherapy as a routine, or planned courses of maintenance chemotherapy are of no proven value. At present, no clear recommendations for the management of patients with a partial response, and clinical evidence of continued disease activity after six courses of treatment can be made. An occasional patient without significant toxicity and evidence of continuing response from course to course may benefit from further courses of treatment, but in general, the patients' best interests may be served by treatment discontinuation, with a period of time off therapy before clinical relapse occurs.

WHAT IS THE OPTIMAL MANAGEMENT OF THE RELAPSED PATIENT?

Patients with relapsed disease after an initial induction treatment unfortunately comprise the majority of patients with stage III and IV ovarian cancer. Three groups can be recognised, (a) those whose initial treatment was unsuccessful insofar as a sustained response was not seen and treatment progression was evident despite continuing therapy. Such patients have a very poor prognosis, and if further chemotherapy is offered this could include taxol or another experimental phase II agent. Palliative radiotherapy may be beneficial; palliative surgery is unlikely to be useful. (b) Those whose initial treatment resulted in an apparent complete response (clinical or pathological), but who then developed evidence of disease relapse some time later. The longer the interval off therapy, the more likely is the patient to respond to repeated chemotherapy with the same or similar agents, e.g. cisplatin or carboplatin, assuming either was used in induction treatment. Treatment-free intervals of less than 12 months, 13–24 months and > 24 months are associated with "second chance" response rates of 27, 33 and 59%, respectively [19]. Treatment choices can, therefore, be made accordingly on an individual patient basis. An occasional patient, particularly with a long treatment-free interval may benefit from salvage

surgery if investigations suggest an isolated relapse, but such cases are exceptional.

The fact is that patients with relapsed ovarian cancer are not curable and increasingly aggressive treatment is not appropriate. On the other hand extended periods of disease-free survival can be achieved in association with a good quality of life by skilful management at this stage. Common problems which present themselves include recurrent ascites, and here intraperitoneal chemotherapy may possibly be useful, although for a very troublesome case the insertion of a Leveen shunt may be more beneficial.

(c) An occasional patient with relapsed disease can have quite an extended survival, despite the presence of a very bulky tumour. Such disease is often histologically well differentiated and repeated courses of chemotherapy may not necessarily be appropriate. Such cases are unusual, but hormone therapy, e.g. with tamoxifen or progestogens may play a role in the management of such patients. The documented response rate in hormone therapy is in the range of 10–15% [20] and the selection of patients who may benefit from this approach is a matter of careful clinical judgement.

WHAT ARE THE LONG-TERM RESULTS OF TREATMENT?

A question frequently asked of clinicians dealing with ovarian cancer relates to the likely outcome in terms of long-term survival. Can one talk in terms of "cure" in the era of platinum-based chemotherapy?

For the answer, we should be grateful to colleagues from The Netherlands who have provided the most comprehensive data on long-term results from treatment, in patients who entered randomised trials beginning in 1980. Their data do lead to some optimism, since it is evident that a subgroup of patients with stage III or IV disease can be identified who have the potential for long-term survival [21]. With a median follow-up of 9.5 years, 21% of patients who received a cisplatin-containing combination are alive. The most important predictors for long-term survival include the use of cisplatin, a complete response at a second laparotomy, and differentiation (Broder's) grade of the tumour.

Patients who do not reach a complete response after initial chemotherapy have a relatively poor outlook, as do patients with bulky residual disease after the initial surgery, prior to the start of chemotherapy. For this reason, the conventional recommendation is to attempt maximal tumour debulking at the time of the initial surgery, and this is widely practised, at least by trained gynaecological oncologists. Recent questions, however, have been raised regarding the practice. The hypothesis has been put forward that if the disease when it presents is "debulkable", often appearing in fairly large masses rather than as multiple small tumour nodules, then such disease may be biologically more favourable anyway, with a less aggressive natural history and a better overall survival expectation, than disease which is not debulkable and which carries a worse prognosis because of an intrinsically more aggressive, possibly drug-resistant, biological behaviour. Clinical trials which will aim to test this hypothesis are under way; meanwhile, it is clearly appropriate for practising oncologists to continue to recommend that maximal tumour debulking should be the aim prior to the start of chemotherapy.

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