The *neu*-oncogene protein as a predictive factor for haematogenous metastases in breast cancer patients. *Int J Cancer* 1990, **45**, 55–58.
11. Hennessy C, Henry JA, May SEB, Westley BR, Angus B, Lennard TWJ. Expression of the anti-metastatic gene nM23 in human breast cancer: an association with good prognosis. *J Natl Cancer Inst* 1991, **83**, 281–285, 1991.
12. Hart IR, Goode NG, Wilson RE. Molecular aspects of metastatic spread. *Biochem Biophys Acta* 1989, **989**, 65–84.

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Ovarian Cancer Treatment: Time for Some Hard Thinking

INTRODUCTION

THE RESULTS of several carefully designed studies of the treatment of epithelial ovarian cancer are now available. As a consequence, we can modify the treatment strategy for such patients. Until now, the treatment plan for patients with disease outside the pelvis or distant metastasis (FIGO stage III and IV) included extensive surgical cytoreduction followed by chemotherapy with one to four drugs, restaging by ultrasound and computed tomography and a second laparotomy to restage or to remove remaining tumour. When tumour was present additional treatment was started. During follow-up, repeated ultrasound and computed tomography were used to detect relapse. For most of the parts of the treatment plan, recent studies have highlighted new facts and it is time for some hard thinking about whether we should change the treatment policy. The role of surgery, the choice of cytotoxic treatment, follow-up and treatment of relapse are aspects that deserve attention.

SURGERY

The surgical removal of as much tumour as possible during the initial laparotomy has long been part of the standard treatment. Protocols to resolve the influence of primary cytoreduction on survival were doomed to failure because of poor accrual of patients. One of the reasons for the low enthusiasm for such protocols is that when the abdomen is open for diagnostic purposes, debulking to tumour remnants of less than 1–2 cm is feasible in most cases without complications. Data from the Netherlands Joint Study Group for Ovarian Cancer show that removal of tumour down to microscopic disease results in 5 and 10 year survival rates of 62% and 37%, respectively. However, in patients with tumour remnants of more than 5 cm, the corresponding rates are 13% and 9%. Similar data have been presented by others, and primary cytoreductive surgery has therefore been accepted as part of the treatment plan.

More controversial is the role of intervention surgery (removal of tumour as soon as chemotherapeutic reduction renders the tumour masses resectable). Intervention surgery is most likely worthwhile in patients who had a biopsy only at first surgery, but not in patients who underwent a serious attempt at cytoreduction [1]. A randomised study of the EORTC to resolve this question is underway and the results will need to be taken into account before the role of intervention surgery as part of standard treatment can be defined.

The case is different for second-look surgery (exploratory laparotomy to assess the cancer status of a patient who has completed chemotherapy and is clinically free of disease). There is no place for this type of surgery. For, as we know, the detection of tumour at second-look laparotomy will not lead to the start of treatment alternatives with survival benefit. Those who state that second-look surgery can be accepted as part of research protocols have to consider that it is ethically questionable to perform a surgical procedure for research purposes only.

CHEMOTHERAPY

Cytotoxic treatment is the cornerstone in the treatment of advanced disease. With the addition of cisplatin to an alkylating agent about 80% of the patients respond and experience relief of symptoms and prolonged progression-free survival. With cisplatin-based combinations, the overall 5 year survival rates have been improved from 18% to 32%, with 21% of the patients alive at 10 year follow-up [2]. These results have been the basis of accepting these combinations as the initial standard treatment.

Carboplatin is thought to be as effective as cisplatin, but less emetogenic, and almost not nephrotoxic or neurotoxic. But caution should be exercised about replacing cisplatin in combinations for ovarian cancer and accepting carboplatin-based treatment as a new standard [3]. Long-term data from comparative studies are lacking, and only a few studies have been reported in detail so far. A disadvantage of carboplatin is that it is myelotoxic, and when carboplatin and cisplatin are compared at equitoxic myelosuppressive dosages, cisplatin treatment gives significantly better overall survival [4].

The results of studies comparing carboplatin in optimal dosage with cisplatin are difficult to interpret because patients randomised to receive carboplatin are subsequently treated with cisplatin and *vice versa*. This crossover from one treatment to the other before resistant disease emerges influences outcome in terms of progression-free and overall survival. In addition, the progression-free survival in these studies is calculated from the date of first surgery to the date of first progression, irrespective of whether progression occurred during carboplatin treatment or during subsequent cisplatin treatment. Survival is also a result of the activity of both carboplatin and cisplatin. That crossover is indeed not rare is illustrated in a large Italian study [5]. All patients with residual disease at second-look laparotomy and those with stable disease after three courses were crossed over to the alternative treatment, accounting for almost 60 out of the 82 carboplatin patients.

In ovarian cancer a dose-response relation is likely, and adjusting the dosage of carboplatin or delaying treatment cycles to permit recovery of leucocytes and platelets may diminish the results. This may be the reason that two large studies comparing

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carboplatin with cisplatin produced response rates in favour of cisplatin. In the Italian study with the single drugs, 73% (59/81) of the patients responded to cisplatin and 61% (50/82) to carboplatin [5]. When the drugs are combined with other myelosuppressive agents, dose adjustments or delay between treatment cycles may be necessary. Delay between treatment cycles was allowed in an EORTC study comparing carboplatin with cisplatin as part of a combination regimen. In this study the overall response rate achieved with the cisplatin regimen was 63% (69/110) and 48% (57/118) with the carboplatin combination [6]. An advantage of cisplatin is that a dosage of 75–100 mg/m^2 can be maintained for at least six cycles of treatment at nearly 100% of the planned dose, even when combined with myelosuppressive agents. This may turn out to be crucial. The message is that we have to await more mature data before deciding to replace cisplatin with carboplatin.

FOLLOW-UP AND RETREATMENT

Monitoring treatment and follow-up after patients achieve a remission is easier since the introduction of CA125 measurement. Assay of CA125 levels must be part of the staging procedure and intermittent measurements are recommended, preferably twice a month during treatment. In patients with elevated CA125 values at the start of treatment, the decrease of marker levels correlates with tumour regression and as long as no rise in blood levels is seen, progressive disease can virtually be excluded. The use of CA125 measurement for the follow-up of patients after treatment also holds promise. Repeated diagnostic imaging is no longer necessary and recurrent tumour can be detected earlier in the course of the disease. CA125 levels may rise several months (median 4.5) before other signs of progression are clinically detectable [7]. Although not proven, we may assume that early detection of relapse will mean that the tumour is smaller and thus more easy to control with reinduction treatment.

For reinduction, carboplatin with or without cyclophosphamide is attractive. This combination can result in remission rates as high as 30–70%, lasting for half a year or more, and can provide palliation with a good quality of life [8]. Dose intensity is of less importance in the palliative setting. Accordingly the prolonged interval between treatment cycles because of myelosuppression is not a major problem. In this journal Van der Burg *et al.* [8] have reported that retreatment with a carboplatin regimen is more successful when the interval between the last treatment and diagnosis is more than 1 year. With the addition of the CA125 assay, this period may be considerably shorter. Although the schedule with oral cyclophosphamide used by Van der Burg *et al.* is feasible, the intravenous administration of cyclophosphamide as a single dose is probably easier and more convenient. Because the treatment is well tolerated, we could consider offering all patients who relapse after a treatment-free period of any length this combination for at least two courses. This is especially attractive for patients in whom tumour response can be followed up with CA125 measurement.

CONCLUSIONS

As a result of research in the past decade, it is time to simplify our treatment strategy for ovarian cancer. After an initial attempt at cytoreduction, further surgical treatment probably does not provide survival benefit. First-line treatment with cisplatin and cyclophosphamide should be standard, for the time being. Adding more drugs appears to be without benefit. For patients with an elevated CA125 level at the start of treatment, follow-up is easy and can be done with this marker alone, avoiding repeated computed tomography or ultrasound. CA125 has gained a place in the follow-up of ovarian cancer and deserves inclusion in the WHO response definitions. Retreatment for relapse with carboplatin with or without cyclophosphamide after a treatment-free period is attractive. The position of carboplatin as part of the initial treatment has not been established yet. The data from several large studies have to mature before a final decision can be made about carboplatin.

With the current cisplatin-based chemotherapy the 10 year survival rates have doubled. Optimism is justified since promising new drugs, such as taxol, and the improvement of supportive measurements with growth factors and neuroprotective agents may further improve the results of treatment.

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1. Neijt JP, Ten Bokkel Huinink WW, Van der Burg MEL, *et al.* Randomized trial comparing two combination regimens (CHAP-5 v CP) in advanced ovarian carcinoma. *J Clin Oncol* 1987, 5, 1157–1168.
2. Neijt JP, Ten Bokkel Huinink WW, Van der Burg MEL, *et al.* Long term results of chemotherapy in advanced (FIGO stages III or IV) ovarian cancer. Proceedings of the International Gynecological Cancer Society Biennial Meeting, Cairns, 1991 (in press).
3. McGuire WP, Abeloff MD. Carboplatin substitution for cisplatin in the treatment of ovarian carcinoma—a word of caution. *J Natl Cancer Inst* 1989, **81**, 1438–1439.
4. Edmonson JH, McGormack GM, Wieand HS, *et al.* Cyclophosphamide-cisplatin versus cyclophosphamide-carboplatin in stage III–IV ovarian carcinoma: a comparison of equally myelosuppressive regimens. *J Natl Cancer Inst* 1989, **81**, 1500–1504.
5. Mangioni C, Bolis G, Pecorelli S, *et al.* Randomized trial in advanced ovarian cancer comparing cisplatin and carboplatin. *J Natl Cancer Inst* 1989, **81**, 1464–1471.
6. Ten Bokkel Huinink WW, Van der Burg ME, Van Oosterom AT, *et al.* Carboplatin in combination therapy for ovarian cancer. *Cancer Treat Rev* 1988, **15**, 9–15.
7. Van der Burg MEL, Lammers FB, Verweij J. The role of CA125 in the early diagnosis of progressive disease in ovarian cancer. *Ann Oncol* 1990, 1, 301–302.
8. Van der Burg MEL, Hoff AM, Van Lent M, Rodenburg CJ, Van Putten WLJ, Stoter G. Carboplatin and cyclophosphamide salvage therapy for ovarian cancer patients relapsing after cisplatin combination chemotherapy. *Eur J Cancer* 1991, 27, 248–250.