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Perspectives and Commentaries

Current Status of Chemotherapy for Ovarian Carcinoma

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(A COMMENT ON: Piccart MJ, Speyer JL, Wernz JC *et al.* Advanced ovarian cancer: 3 year results of a (6–8 month) 2 drug cisplatin containing regimen. *Eur J Cancer Clin Oncol* 1987, **23**, 631–641.)

ALTHOUGH systemic combination chemotherapy is widely accepted as the treatment of choice for patients with advanced epithelial cancer of the ovaries stages III and IV, even IIB, no standard treatment has emerged so far. Many questions remain to be solved and new techniques explored before a clear set of guidelines can be established. Which drugs are best, in which combinations, at which doses, by which route and for how long? Is aggressive toxic chemotherapy worthwhile trying in patients with bad prognostic criteria, such as stage IV disease? Specifically should cisplatin, a toxic drug, be given to any patient with ovarian cancer who might, it is claimed, live just as long with a simple regime of oral alkylating agents? In a recent issue of *European Journal of Cancer and Clinical Oncology*, Piccard *et al.* of the New York University Medical Center [1] reported their results with combination chemotherapy in patients suffering from advanced ovarian cancer. Notwithstanding the limited number of patients treated and the non-randomized design of their study, the data attract interest because only two drugs were used including a relatively high dose of cisplatin (100 mg/m^2 over 5 days). Two large randomized studies from the Netherlands also favour such a high dose of cisplatin [2, 3]. Perhaps the lack of difference between single agent chemotherapy and cisplatin based regimens with regard to survival is related to the dose of cisplatin. Ozols and Young [4] gave very high doses of cisplatin to patients with disease resistant to conventional doses and reported encouraging remissions. In their analysis Levin and Hryniuk [5] evaluated 33 first-line treatment regimens for the relationship between dose intensity and treatment outcome. Dose intensity and number of drugs used correlated significantly with clinical response and survival ($P < 0.001$). The interaction between number of drugs used and dose intensity was more significant than either variable alone for clinical response ($P < 10^{-5}$) and survival ($P < 10^{-5}$). No correlation between dose intensity and clinical response for cyclophosphamide or doxorubicin could be shown, whereas this correlation was significant for cisplatin ($P < 0.001$). Further, the average median survival time for multi-agent regimens not containing cisplatin was 14 months in contrast to the mean survival time for cisplatin-containing regimens of 24 months. The mean survival time for single alkylating agent regimens of 12 months was not improved by higher dosages. Cisplatin emerged as the most active drug in the multi-agent chemotherapy regimens studied, and it seems that high doses may be most effective if given in first-line. Now comes the problem of toxicity.

The incidence of neurotoxicity and nephrotoxicity increases dramatically when dosages of 100 mg/m^2 or more of cisplatin are administered for long periods. Such schedules are only warranted if this aggressive treatment can be translated into cure of a significant proportion of the patients or if we are in the future able to ameliorate the toxicity spectrum. Chelating agents like thiosulphate [6] and diethyldithiocarbamate [7] are currently being studied for their protective role against nephrotoxicity, and a study to evaluate the prophylactic use

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of a vasopressin analogue against neurotoxicity has just been launched in the Netherlands based on *in vitro* studies [8]. Until results of these studies prove otherwise a maximum dose of 100 mg/m^2 of cisplatin should be recommended in daily practice.

Hexamethylmelamine and doxorubicin are two other drugs frequently used in combination chemotherapy in ovarian cancer regimens. What these two drugs really contribute (apart from toxicity) remains uncertain. No clinical studies are available proving that hexamethylmelamine adds an antitumour effect to a combination of cisplatin and cyclophosphamide [9]. No improvement of survival could be attributed to doxorubicin in Italian studies [10] and a study published by a Danish group [11], again in combination with cisplatin plus cyclophosphamide. A trial in the Netherlands Joint Ovarian Cancer Study Group failed to show any effect of the addition of hexamethylmelamine and doxorubicin to cisplatin and cyclophosphamide [3]. Based on these data cisplatin and cyclophsophamide emerge as the two standard drugs at this moment for the treatment of ovarian cancer as is illustrated by the study of Piccart *et al.* in a previous issue.

Which horizons will open in the near future in this disease is of course a matter of speculation. The disappointing long-term results, even in patients achieving complete remission, the relapse rate is as high as 50%, suggest seeking a less toxic and more effective treatment. Carboplatin and iproplatin are analogues of cisplatin effective against ovarian cancer. Preliminary analysis of carboplatin used in combination suggest that it is equally effective as cisplatin and far less toxic (however, far more expensive). The study of the Gynecological Cancer Cooperative Group (GCCG) of EORTC compared carboplatin and cisplatin in the CHAP-5 regimen (with doxorubicin, hexamethylmelamine and cyclophosphamide) [12]. The follow-up time is, however, very short. If these results hold up, out-patient treatment for ovarian cancer patients may thus become available since no hyperhydration is needed for carboplatin and the overall toxicity is mild.

The problem of increasing antitumour effects has not been solved by using cisplatin analogues at conventional doses, and as higher doses may overcome resistance to conventional dosages, this approach is being intensively studied. High dose cisplatin is not pratical because of high toxicity. High dose carboplatin may be effective in overcoming drug resistant. The toxicity profile mainly consisting of myelosuppression (very severe thrombocytopenia) changes, however, as neurotoxicity and ototoxicity at a dose of 800–1600 mg/m^2 become evident. Nevertheless, higher dosages of carboplatin may play a role in the near future in aggressive treatment strategies in high-risk ovarian cancer patients.

High doses may be achieved via the intraperitoneal route. This is relevant in ovarian cancer, as the tumour is mostly confined to the abdominal space. Intraperitoneal chemotherapy has, however, not yet been proven of value, since no randomized studies are available. Very preliminary experience in the United States and Europe evoke some enthusiasm, but the burden of the technique restricts its use to the experimental setting and it is not recommended for daily practice [13].

What conclusions should we draw from the curently available data for our day-to-day routine? I think that a combination of cisplatin and cyclophosphamide should be chosen, if, as is pointed out and illustrated by the study presented by Piccart *et al.*, an adequate dose of cisplatin of 75–100 mg/m^2 is given. In patients suffering from ovarian cancer, stage IV, a bulky mass after cytoreductive surgery, a low Karnofsky scale and other bad prognostic signs, single agent chemotherapy or a less toxic combination of carboplatin in combination with cyclophosphamide may be applied. In these patients palliation rather than a complete remission should be pursued. In stage III patients a higher complete remission rate and prolonged survival may result from the current treatment strategy in ovarian cancer; the goal of cure in the vast majority of patients is still far away.

REFERENCES

1. Piccart MJ, Speyer JL, Wernz JC *et al.* Advanced ovarian cancer: 3 year results of a (6–8 month) 2 drug cisplatin containing regimen. *Eur J Cancer Clin Oncol* 1987, **23**, 631–641.
2. Neijt JP, ten Bokkel Huinink WW, van der Burg MEL *et al.* Randomised trial comparing two combination chemotherapy regimens (Hexa-CAF vs. CHAP-5) in advanced ovarian carcinoma. *Lancet* 1984, **2**, 594–600.
3. Neijt JP, ten Bokkel Huinink WW, van der Burg MEL *et al.* Combination chemotherapy with CHAP-5 and CP in advanced ovarian cancer, a randomised trial of the Netherlands joint study group for ovarian carcinoma. *Proc Am Soc Clin Oncol* 1985, **4**, 114.
4. Ozols RF, Behrens BC, Ostchega Y, Young RC. High dose cisplatin and high dose carboplatin in refractory ovarian cancer. *Cancer Treat Rev* 1985, **12** (Suppl A), 59–65.
5. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy of advanced ovarian carcinoma. *Proc Am Soc Clin Oncol* 1986, **5**, 112, abstr 435.
6. Howell S, Pfeifer C, Wang W *et al.* Intraperitoneal cisplatin with systemic thiosulphate

protection. *Ann Intern Med* 1982, **97**, 845–851.
7. Borch RF, Bodenner DL, Katz JC. Diethyldithiocarbamate and cisplatinum toxicity. In: Hacker MP, Douple EB, Krakoff IH, eds. *Platinum Coordination Complexes in Cancer Chemotherapy*. Boston, Martinus Nijhoff, 1984, 154–164.
8. Do Koning P, Neijt JP, Jennekens FGI, Gispen WH. An ACTH (4–9) analog prevents cisplatin neurotoxicity in rats. *Proceedings of the Fifth NCI-EORTC Symposium on New Drugs in Cancer Therapy*. Amsterdam, The Netherlands, 1986, Vol. 1, 32.
9. Foster BJ, Clagett-Carr K, Marsoni S, Simon R, Leyland-Jones B. Role of hexamethyl melamine in the treatment of ovarian cancer: where is the needle in the haystack? *Cancer Treat Rep* 1986, **70**, 1003–1014.
10. Conte PF, Bruzzone M, Chiara S *et al.* A randomized trial comparing cisplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide versus cisplatin, doxorubicin and cyclophosphamide in advanced ovarian cancer. *J Clin Oncol* 1986, **4**, 965–971.
11. Bertelsen K, Andersen JE, Jakobsen A, Sell A, Stroyer I, Panduro J. A randomized study of CP versus CAP in advanced ovarian cancer. *Proc Eur Soc Med Oncol Cancer Chemother Pharmacol* 1986, **18**, 7.
12. ten Bokkel Huinink WW, van der Burg MEL, van Oosterom AT. Carboplatin replacing cisplatin in combination chemotherapy for ovarian cancer. A large scale randomized phase III trial of the Gynecological Cancer Cooperative Group of EORTC. *Proc Am Soc Clin Oncol* 1987, abstract 465.
13. ten Bokkel Huinink WW, Dubbelman R, Aartsen E, Franklin H, McVie JG. Experimental and clinical results with intraperitoneal cisplatin. *Semin Oncol* 1985, **12**, 43–46.