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Elevated Serum CA-125 Levels in Patients with Ovarian Fibrothecomas

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TO DATE, CA-125 is the best tumour marker for ovarian adenocarcinoma [1]. It has been found to be especially useful for monitoring the response to treatment of ovarian carcinoma patients with initially elevated CA-125 levels. Of them, 90–100% will have persistent ovarian cancer at second-look laparotomy if their serum CA-125 fails to decline during treatment [2]. However, up to 50% will still have residual disease despite normal CA-125 levels, although in these cases the residual tumour is usually minimal [2].

Unfortunately, ovarian cancer is not the sole condition associated with elevated serum CA-125 levels. Other gynaecological cancers arising from the celomic epithelium (fallopian tube, endometrium, endocervix), non-gynaecological cancers (pancreatic, hepatic, breast, colon and lung), as well as pancreatitis, peritonitis, renal failure and liver cirrhosis, together with some benign gynaecological diseases (pelvic inflammatory disease, endometriosis) have all been associated with abnormal elevation of CA-125 [3]. This limits its usefulness as a screening tool for ovarian cancer in asymptomatic patients. Even in the presence of clinical signs suggestive of ovarian carcinoma, a high serum CA-125 is still not necessarily indicative of the disease. We have performed serial determinations of serum CA-125 levels in 6 consecutive patients with benign ovarian fibrothecomas diagnosed and treated at our hospital during the last 2 years. Initial serum CA-125 was invariably elevated in all patients before surgical treatment, in some of them extremely so (above 500 U/ml, which is the top limit at our laboratory). Serum levels had returned to normal in all patients after a maximum of 6 months following surgical excision (Fig. 1). The elevation of CA-125 in these patients seems to be associated with the proliferation of the rather inert fibrous stromal component of their tumours, since 1 patient with a pure ovarian thecoma diagnosed during the same period showed normal pretherapeutic CA-125 levels. The hypothesis is further supported by the findings of Walker *et al.* [4], who reported about 2 cases of ovarian cellular fibromas associated with an elevated CA-125. To corroborate it, we determined CA-125 serially in 5 patients subject to controlled ovarian hyperstimulation as part of an *in vitro* fertilisation program. Gonadotrophin hyperstimulation, as practised on these patients, often produces massively enlarged ovaries by acting mainly on the granulosa-cell population of them, and only secondarily affecting the inert stromal component. All 5 patients (data not shown) showed normal (below 30 U/ml) prestimulation and serial CA-125 levels throughout their stimulation cycles, also at the point of maximal stimulation, as determined by means of oestradiol plasma levels and ultrasound examination of follicle growth.

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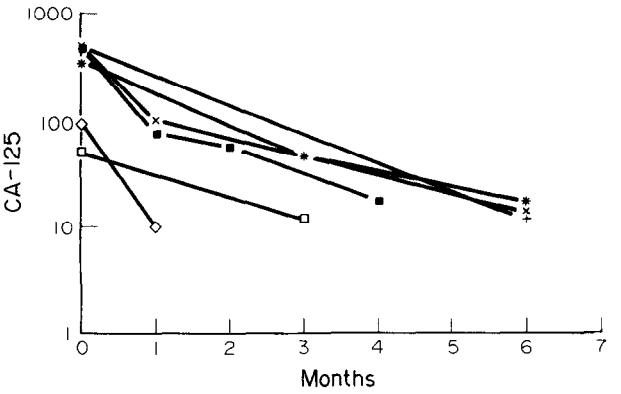

Fig. 1. Decline of CA-125 levels, expressed in U/ml on the *y*-axis, after surgical excision of the tumour. All values below 20 U/ml after a maximum of 6 months.

Ovarian fibrothecoma, thus, which is one of the most benign and well-differentiated tumours arising in this organ, consistently elevates serum CA-125. In view of this fact, it is remarkable that CA-125 expression has been found to be inversely correlated with the degree of differentiation of cultured ovarian carcinoma cells, as reported by Brooks *et al.* [5]. One explanation for this may be that mesothelial tumour cells behave quite differently from fibrous stromal cells regarding the expression of CA-125, even if belonging to the same organ.

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Fotemustine–Dacarbazine Combinations in the Treatment of Metastatic Melanoma

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AAMDAL *ET AL.* [1] have recently reported encouraging results with dacarbazine and fotemustine used sequentially for meta-

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static malignant melanoma (MM). The schedule included 4-week courses of dacarbazine 500 mg/m^2 followed 3 h later by fotemustine 100 mg/m^2. The overall response rate (RR) of 33% [16.5% complete response (CR) and 16.5% partial response (PR)] may represent an advance in the management of this presently incurable disease. The best responses were observed in lung metastases (7/14 cases), liver (3/5 cases) and nodes (5/6 cases). Skin and brain metastases responded poorly (1/4 and 0/4 cases, respectively). The reported haematological toxicity was mild to moderate in 20/24 patients, and severe in 1 case. Unexpected fatal pulmonary toxicity occurred in 1 patient.

We have already reported our results using these drugs in the treatment of MM [2, 3]. Non-randomised comparison reveals substantial differences. In our study all the responses were observed in those who were treated with the alternated combination (fotemustine on days 1 and 8, dacarbazine on days 15 and 16). No response was observed in 3 patients treated with the sequential protocol. In our series the overall RR was 8.3%, much lower than the figure of 33% reported by Aamdal *et al.* [1]. The responses included one PR in brain metastases for 4 months, and one PR in brain with CR in lymph nodes for 4 months. There was one minimal response (MR) in brain and stomach with PR in lymph nodes for 8 months, and stable disease (SD) for 2 and 4 months in 2 patients in whom progressive disease was documented prior to treatment induction.

The response in the brain in our patients was of particular interest. The overall response rate for brain metastases (complete and partial) was 22.2% with a median duration of 4 months, including CR in 1 patient for 3 months and PR in 3 patients for 4 months each. Minimal response was observed in 1 patient for 6 months, and stabilised disease in 2 patients for 1 and 4 months. The response in visceral or peripheral lesions was poor, compared with the 33% reported by Aamdal *et al.* [1]. In our series no pulmonary toxicity was observed in the 23 treated patients [2, 3].

The difference in response between the two schedules may be explained by the fact that the sequential administration is based on early inhibition of O^6 alkyltransferase (O^{6}AT) by dacarbazine. This schedule seems to be better for peripheral or visceral lesions. In the alternating administration, dacarbazine and fotemustine were given on separate days. The latter schedule appears to be more active in brain metastases.

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Correction

Anticancer Drug Screening and Discovery in the 1990s: A European Perspective.—In this article by G. Schwartsmann and P. Workman (Vol. 29A, pp. 3–14), the following references were unfortunately omitted from the bibliography:

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