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Initial Experiences with Serum Alkaline DNase Activity in Monitoring the Effects of Therapy for Carcinoma of the Uterine Cervix

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The objective was to evaluate if variations in serum alkaline DNase activity (SADA) can predict the effects of therapy in women with early stages of primary cervical carcinoma. 29 out of 33 patients had no evidence of disease after therapy. Only 5 out of the 29 women showed increased SADA levels after therapy compared with the pretreatment SADA value. Of the 4 women with evidence of disease after therapy, 3 had unchanged or decreased SADA levels. We conclude that serum alkaline DNase activity seems to have little to offer in predicting the effects of treatment in stage I and stage II cervical carcinoma.
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INTRODUCTION

RECENT REPORTS indicate that serum alkaline DNase activity (SADA) can be of value in predicting the effects of therapy in patients with various malignant diseases [1–3].

An increase in SADA values after therapy, compared to pretreatment SADA levels, is supposed to correspond to a complete tumour regression. If the SADA level is lower than the initial SADA value, only a partial tumour regression is seen. No variation in SADA indicates no response to treatment [1]. After transplanting tumour cells to rats, the obtained decrease in SADA preceded the appearance of any palpable tumour mass by 4–5 days [4]. These findings encouraged us to perform the present investigation.

PATIENTS AND METHODS

Patients

The study comprised 33 patients with primary cervical carcinoma and 30 apparently healthy female volunteers (mean age was 47 and 49 years, respectively).

All patients were staged in accordance with the International Federation of Gynecology and Obstetrics (FIGO) classification [5]. Patients with stage Ib ($n=22$) and stage IIa ($n=6$) disease were treated by preoperative intracavitary radium applications followed by radical hysterectomy with pelvic lymphadenectomy. Elderly women received radiotherapy alone. Patients with stage III ($n=3$) and stage IV ($n=2$) disease were treated with radiotherapy, sometimes in combination with chemotherapy. The 4 patients with evidence of disease after therapy had little regression of the tumour.

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Analytical procedures

Blood samples were collected prior to treatment and 1–5 months after therapy. In the control women, blood was drawn in the morning after breakfast during 3 days. Serum was stored at −20°C until analysed and serum samples taken from each woman were analysed simultaneously in a single assay.

For the detection of SADA (EC 3.1.4.5), a spectrophotometric technique as described by Loiselle and Carrier [6] was used. Briefly, the assay tubes, containing 100 μl of serum sample, 500 μl test buffer (0.2 mol/l Tris HCl buffer containing 0.5 mol/l $CaCl_2$ and 10 mmol/l $MgCl_2$) and 400 μl calf thymus DNA (D-1501, purchased from Sigma) solution, were incubated at 55°C for 60 min. Thereafter, 500 μl of 60% magnesium sulphate solution and 1.5 ml of 70% perchloric acid solution were added. The mixtures were incubated in an ice bath for 60 min and centrifuged at 2000 *g* for 20 min. The liberated oligonucleotides were measured at 260 nm against a blank containing EDTA. Three standard enzyme preparations (9, 39 and 52 kU/l[7]) were used. The intra-assay and interassay coefficients of variation were below 11% and 15%, respectively.

RESULTS

Pretreatment SADA levels varied between 9 to 70 kU/l (Fig. 1). Mean (S.E.) value was 37 (3.0) kU/l.

The overall range of SADA levels among the controls was 3–78 kU/l. Mean SADA values on the consecutive days A, B, and C were 28, 30 and 34 kU/l, respectively. No significant difference ($P=0.07$) was found between pretreatment SADA values in patients and SADA levels on day A (lowest SADA concentration) in healthy controls (unpaired Student's *t* test).

The intraindividual coefficient of variation (CV) of SADA (based on the three samples) for each control woman was calculated and ranged between 3.5% and 69.8%. The mean CV was 21% and the 95% confidence interval between 15.7% and 26.5%.

Among the 29 women who had no evidence of disease after therapy, mean pretreatment and post-treatment SADA values

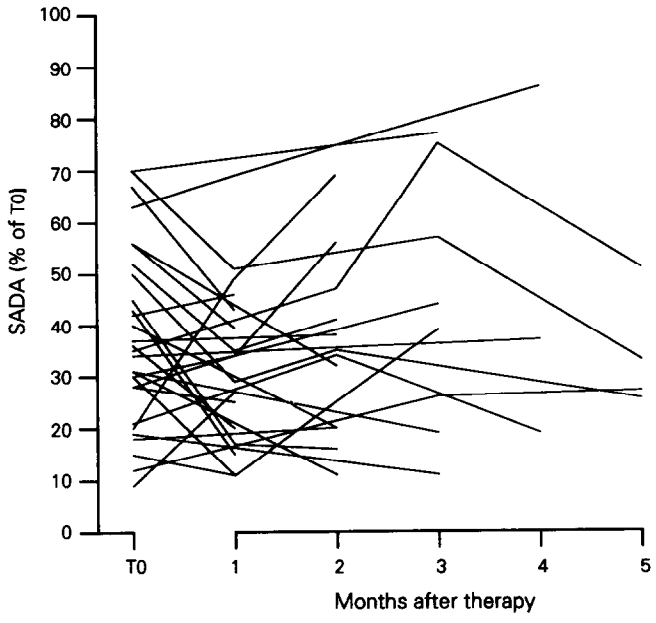

Fig. 1. Serum alkaline DNase activity (SADA) before treatment (T0) and after treatment, in 29 patients with no evidence of cervical carcinoma after therapy. In 12 women 2–3 post-treatment SADA values were available over a period of 5 months. No evidence of disease was defined as the complete disappearance of all objective evidence of tumour. None of these women had a relapse within the following 12 months after treatment.

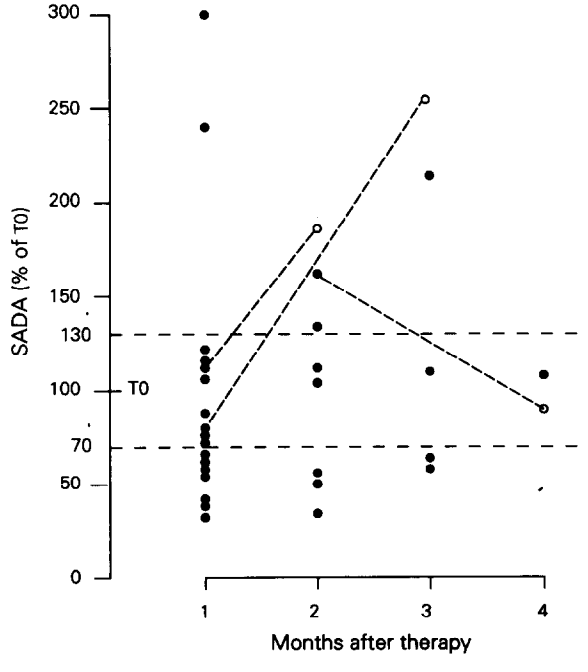

Fig. 2. Relative variations in serum alkaline DNase activity (SADA) in the 29 patients with no evidence of cervical carcinoma after therapy. The pretreatment value (T0) in each patient is considered as 100%. (●) The first blood sample drawn after therapy. In 3 (○) of the 12 patients in whom SADA was repeatedly available, SADA exceeded a 30% deviation from the T0 value.

were 38 and 32 kU/l, respectively ($P=0.07$, paired Student's t test).

In the 4 patients with residual tumour, mean SADA levels before and after therapy were 30 and 20 kU/l, respectively.

Each patient was individually evaluated in terms of comparing SADA levels after treatment with the pretreatment SADA value (Fig. 1). A change in SADA exceeding 30% of the pretreatment value was considered to be different from changes due to physiological variations. Among the 29 women with no evidence of disease, 5 showed more than a 30% increase in SADA concentrations. 12 out of the 29 women had decreased SADA levels after therapy (Fig. 2).

In 12 out of the 29 women, blood samples were collected 2–3 times after therapy (Fig. 1). The intraindividual CV of SADA in these 12 patients after therapy varied between 2.7% and 73.5%. Mean CV was 24.5%. In 3 patients the CV exceeded 30% (Fig. 2). In the remaining 9 patients little SADA changes were seen over time.

DISCUSSION

As previously reported [1, 2, 8], there was a wide interindividual variation of SADA values, both in our cancer patient group as well as in the control group. This makes the use of a cut-off level less meaningful.

Cancer patients (mainly with advanced stage of disease) have been suggested to have low SADA levels [2, 6, 9]. Other authors have found contradictory results [8, 10, 11]. This difference in results may reflect that SADA is a composite of inhibitor(s) as well as enzyme levels [12–14].

The mean pretreatment SADA value in patients with cervical carcinoma did not significantly differ from the mean SADA levels in the control group. The majority of our patients with cervical carcinoma presented with small tumour volumes which might have contributed to the relatively high mean value of SADA.

The typical variations of SADA levels, as a consequence of treatment, in non-gynaecological malignant diseases [1, 2, 3, 9] could not be found in the present investigation on cervical carcinoma. It is possible that a difference in tumour burden has contributed to the divergence between the results.

Our data in the control women indicates that the intraindividual variation in SADA values is at least 26%. This is in line with previous findings [15]. Based on these results we have considered variations in SADA below 30% as physiological intraindividual variations, whereas Economidou *et al.* considered variations exceeding 15% to be significant [9].

In the majority of our patients, the first post-treatment blood sample was collected 1 month after therapy (Figs 1 and 2). Although, several post-treatment serum samples were available in only 12 patients, changes in SADA values above 30% between the first, second or third blood sample could only be found in 3 patients. It seems unlikely that we have missed (by collecting the blood samples too soon after therapy) the expected increase in SADA levels [1].

We conclude that SADA seems to have little to offer in predicting the effects of therapy in patients suffering from small tumour volumes of cervical carcinoma.

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An Unusual Cause of Diplopia in a Cancer Patient

Antoinette van der Heijden, Albert Twijnstra, Willy P.M.A. Lamers, Pierre S.G.J. Hupperets and Gerard Freling

A 47-year-old woman with metastatic infiltrating lobular carcinoma of the breast developed diplopia. Computed tomography of the orbits showed enlargement and irregularity of the right inferior rectus and inferior obliques muscles. Biopsies of these muscles contained breast carcinoma cells. This case report discusses the causes of diplopia in cancer patients, with special attention to the diagnostic problems of metastasis in extraocular muscles. The possible combined occurrence of metastasis in the leptomeninges and extraocular muscles is also to be borne in mind if the latter diagnosis is not to be missed.
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INTRODUCTION

A SUBSTANTIAL proportion of cancer patients develop neurological complications during the course of their disease [1]. Diplopia in a cancer patient requires neurological evaluation. The most common cause of diplopia in cancer is leptomeningeal metastasis or metastasis to the base of the skull. Metastasis to the brainstem can also cause diplopia, in which case it is usually accompanied by involvement of other cranial nerves or long tracts [2]. Orbital metastasis of solid tumours is rare, and metastasis into the extraocular muscles has seldom been described.

In this report we describe an unusual case of metastasis of breast cancer in two extraocular muscles of the right eye without infiltration of the orbit.

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CASE REPORT

A 47-year-old woman was admitted to the hospital with diplopia in April 1988. She had been well until 5 years earlier, when she had a mastectomy for an infiltrating lobular carcinoma of the left breast. She subsequently underwent adjuvant chemotherpy because of the presence of metastasis in the axillary nodes. She remained well until April 1988, when she developed enlarged left axillary and left cervical nodes. Biopsy confirmed breast cancer. Further examination revealed bone metastasis. She started treatment on tamoxifen and bisphosphonate capsules.

In April 1988 she complained of painless diplopia on left lateral gaze. There were no other neurological symptoms. There was no history of previous neurological problems. On neurological examination the patient was alert and full oriented. Visual acuity and visual fields were normal; optic fundi were normal; pupils were equal in size and reactive. Both orbital regions appeared normal. There was an impaired adduction and downwards gaze of the right eye without ptosis. The external movement of the left eye was normal in all directions. Ocular media were clear. Results of the remainder of her neurological and