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Serum alpha fetoprotein kinetics in hepatocellular carcinoma

A case for cessation of therapy

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Summary. As chemotherapy with adriamycin is accompanied by toxic side effects, early recognition of ineffective treatment is important. Marker kinetics, apparent half-life (AFL) and doubling time (DT), showed that in five patients with advanced hepatocellular carcinoma, adriamycin was ineffective. Failure of the chemotherapeutic regimen was apparent by the third course of treatment.

Introduction

Alpha fetoprotein (AFP) is a normal human fetal serum protein synthesised from the 4th gestational week in the fetal gastrointestinal tract, liver, and yolk sac [3]. Fetal serum levels reach a peak of 2–3 mg/ml between 12 and 14 weeks of gestation, but progressively fall during later gestation and neonatal life; nonetheless, levels above those found in adults may persist up to 6–12 months from birth [12]. Synthesis of this fetal protein after the age of 12 months shows either the presence of increased hepatocyte turnover, as part of a regenerative process, or the induction of neoplasia involving tissues which have the potential in fetal life to synthesise AFP.

AFP is a serum marker for tumours of the hepatic parenchyma, a small proportion of tumours of the foregut, and germ cell tumours containing endodermal or yolk sac elements [10]. AFP is a glycoprotein of molecular weight 65 000 daltons, with a biological half-life of 3.5–6 days [2, 4]. Serum AFP levels are elevated in about 90% of patients with hepatocellular carcinoma, and the level of AFP in serum is proportional to the tumour burden. Mukojma et al. and other workers [1, 6, 8, 9] have stressed the importance of AFP assays in monitoring the progress of the disease in cases of hepatocellular carcinoma and have shown the levels to be proportional to the tumour burden.

Following surgical treatment or chemotherapy, the serum AFP level falls at a rate governed by the biological half-life of the protein and the residual tumour load. Kohn [5] suggested that a prolongation of the apparent half-life (AHL) in excess of the normal (5 days) was indicative of residual tumour and pointed to a greater probability of early recurrence. The AHL affords a rational means of monitoring tumour burden and predicting early recurrence. In situations where the serum AFP level is increasing the doubling time (DT) of serum AFP, assuming exponential growth of the tumour, also provides an index of the rate of tumour growth and appears to be a reliable means of assessing chemotherapeutic failure. Kohn [5] and Thompson et al. [11] have shown the value of AHL of AFP in the management of testicular carcinoma.

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Patients and methods

The five patients were referred for treatment over a 2-year period. Blood was collected for serum AFP determinations before surgery or chemotherapy and at 2-week intervals during treatment. The diagnosis of hepatocellular carcinoma was confirmed by histological examination of the tumour. In each case the marker (AFP) was also demonstrated in tumour sections by means of an immunoperoxidase technique (Fig. 1).

Serum AFP was measured by a single antibody, polyethylene glycol precipitation, radioimmunoassay. ^{125}I-Labelled AFP was obtained from the Department of Obstetrics and Gynaecology, Ninewells Hospital, Dundee, and rabbit antiserum to human AFP from Dakopatts, Copenhagen. The AFP standard was derived from the WHO reference materials 72/227, 1 unit of AFP being deemed equivalent to 1.20 ng. AHL estimations were made according to the formula published by Kohn [5]:

$$\mathrm{AHL} = \frac{0.3 \times t}{\log_{10} C_o/C_t},$$

where C_o is the initial AFP concentration and C_t, the concentration after t days' treatment. The doubling time (DT) was estimated from a similar formula where there was an increase in the AFP level:

$$\mathrm{DT} = \frac{0.3 \times t}{\log_{10} C_t/C_o}.$$

Treatment. At 3-weekly intervals each patient was given adriamycin (60–75 mg/m^2) as a bolus IV, while receiving 5% dextrose by infusion (500 ml) over a period of 1–2 h. Stemetil (25 mg) was administered IV before each dose of adriamycin.

Results

The alpha-fetoprotein kinetics and clinical details of the five patients are summarised in Table 1. The survival time (i.e., interval between diagnosis and death) ranged from 3 to 15.5 months. The AHL of serum AFP ranged from 9.8 days to 216 days, and the doubling times were between

Table 1. Summary of patient details and alpha-fetoprotein kinetics

Age (years)	Sex	Survival (months)	Therapy	Pre-treatment AFP level (μg/l)	AHL	DT
1. 49	F	15.5	ADM	15,000	24.9	140
2. 62	M	7.5	ADM	1,750	216	244
3. 59	M	8.0	S.ADM	700	9.8	49.5
4. 62	F	7.0	ADM	2,800	13.1	16.0
5. 62	M	4.0	ADM	129	–	53.0

S = Surgery; ADM = Adriamycin; AHL = Apparent half life; DT = Doubling time

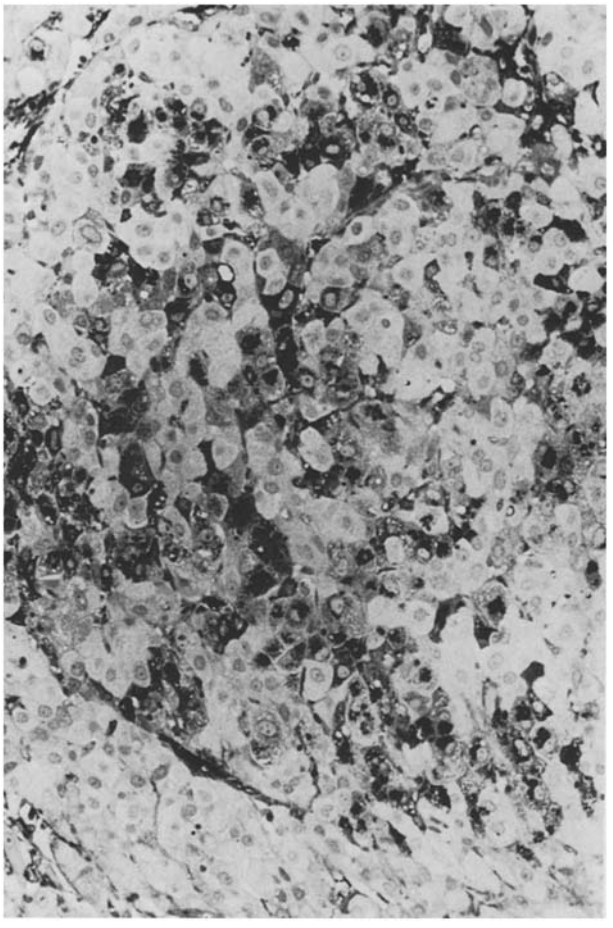

Fig. 1. Hepatocellular cells staining positive for AFP (darkly staining cells) in hepatocellular carcinoma. (Immunoperoxidase stain; ×550)

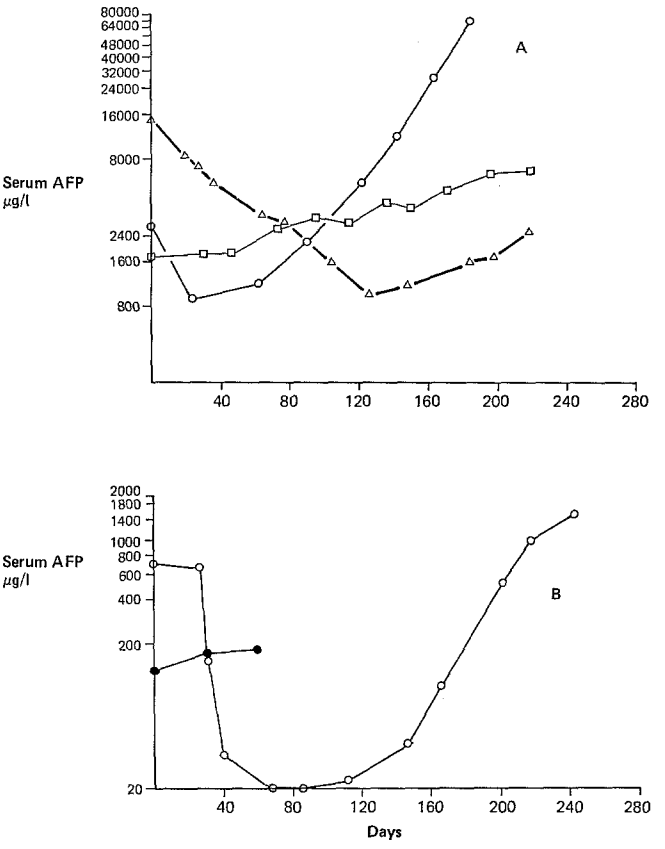

Fig. 2. Serum AFP concentrations in patients receiving chemotherapy with adriamycin. In all cases the drug was administered at 3-weekly intervals. **A** curves for patients 1 (– △ –), 2 (– □ –), and 4 (– ○ –); **B** curves for patient 3 (– ○–), and 5 (– ● –)

16.0 and 244 days. The serum AFP patterns during the course of the disease in all five patients are plotted out in Fig. 2.

The effect of adriamycin on the marker kinetics is illustrated in Fig. 2. In patient 1 (Fig. 2A), the serum AFP level fell to 1/15th of the original value (15 000 μg/l) during the first 120 days of treatment with adriamycin. During the first 60 days the first 60 days the AHL, as calculated from the serum AFP levels of consecutive samplex, was approximately 25 days, suggesting extensive disease. During the next 60 days the AHL increased to 29 days, suggesting either recurrence or resistance to chemotherapy. This was confirmed by the rise in serum AFP level observed at 150 days. Calculation of the DT for serum AFP from 120 days onwards gave a value of 140 days, which is indicative of s slow-growing tumour. In patient 2 (Fig. 2B) the serum AFP level was 1750 μg/l at diagnosis. During adriamycin treatment the serum AFP level continued to rise reaching 6700 μg/l over a period of 220 days. There were two instances when the serum AFP level was lower than in the previous sample. Calculation of the DT gave a value of 244 days, indicating a tumour growing much more slowly than that of patient 1 (Fig. 2A). Thus, the adriamycin therapy seemed totally ineffective in reducing the tumour burden.

Discussion

The serum level of a marker may be of value in assessing the tumour load, and the rate of elimination of the marker following treatment gives an indication of the adequacy of treatment. Observation of marker kinetics allows a verdict on efficiency of treatment with no need to await a return to normal levels [5, 7]. With successful treatment the marker level will fall within its biological half-life. Rates of marker decay (AHL) in excess of the biological half-life suggest the presence of residual tumour. Extension of the AHL during therapy, further refined as a measure of the

tumour doubling time (DT), indicates inadequacy of the therapeutic regimen and the need to change to a different formulation.

In none of the patients in this small series did the AHL approach an adequate rate of decay. All five patients demonstrated patent increase in tumour bulk, with DTs ranging from 16 to 244 days. The longer DT is indicative of low hepatocyte turnover and suggests a slow-growing tumour.

The marker kinetics in these five patients clearly demonstrate the failure of adriamycin therapy. Although the number of cases discussed is not large, it is important to recognise the ineffectiveness of adriamycin therapy, as these unfortunate individuals may rapidly succumb to toxic effects of the drug, such as marrow suprression mucositis and cardiotoxicity, rather than the effect of the tumour burden. The rational use of marker kinetics includes not only the assessment of the effectiveness of a treatment modality but also its possible ineffectiveness. This latter situation should be an indication for cessation of a particular therapeutic regimen.

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