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Actual half-life of alpha-fetoprotein as a prognostic tool in pediatric malignant tumors

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Abstract In a retrospective study, the prognostic value of monitoring the decay of alpha-fetoprotein (AFP) was assessed. Serum AFP was determined serially in 18 children with malignant germ-cell or hepatic tumors: 7 endodermal sinus tumor, 3 embryonal carcinoma, 5 malignant teratoma, 2 hepatoblastomas, and 1 hepatocellular carcinoma. The actual half-life (AHL) of AFP was computed after surgical resection of the tumor. In group 1, which had complete resection and no recurrence during follow-up (n = 13), the AHL of AFP was 4.0 ± 0.9 days. In group 2, which had incomplete resection or recurrence during follow-up (n = 5), the AHL of AFP was 24.8 ± 20 days, significantly longer than that of group 1 (P = 0.0026). The increased AHL of AFP indicated residual active tumor after surgical resection. The AHL of AFP may be more sensitive than serial monitoring of AFP in detecting preclinical recurrence after surgical resection of AFP-secreting tumors. Treatment strategies can be based on AFP clearance, and prospective clinical trials are warranted.

Key words Actual half-life · Alpha-fetoprotein · Malignant germ-cell tumor · Hepatic malignancy

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Introduction

Alpha-fetoprotein (AFP), a major protein of the human fetus, has been found in the serum of patients with hepatocellular carcinoma or hepatoblastoma, and subsequently in a high percentage of patients with malignant germ-cell tumors (GCT). This serum tumor marker is recognized as useful for following the course of malignant GCTs and hepatic malignancies. Changes in serum AFP parallel the clinical course of the disease, and elevation can precede clinical tumor recurrence. However, it may take several weeks to recognize recurrence of the disease by serial follow-up of AFP, because levels usually decrease soon after surgery and only slowly increase later.

Early detection of patients with residual tumor after surgical resection is clearly advantageous so that alternative chemotherapy can be employed. For this reason, we investigated AFP clearance rate as a useful index to detect residual tumor or to predict eventual tumor recurrence. The rate of clearance of tumor markers from patients' serum can be expressed in terms of actual half-life (AHL) [2, 4]. We postulated that the prognosis of a patient could be determined by calculating the AHL after tumor resection. To test this hypothesis, we retrospectively compared the AHL of AFP and clinical courses of 18 children with AFP-producing malignant tumors.

Materials and methods

Children who had been surgically treated for AFP-producing malignant tumors for whom there were enough marker level data for half-life calculations were studied. They were all initially treated with surgical resection at the Severance Hospital from January 1985 on and followed in the same hospital. Clinical data, including type of operation, residual tumor after resection, postoperative treatment, serum AFP levels, and tumor progression or recurrence, were reviewed for all patients. AFP was assayed by a commercial enzyme immunoassay kit (Enzygnost AFP micro, Behring). Serum AFP levels greater than 20 IU/ml were considered abnormal. AHL

for serum AFP was computed in selected patients according to the formula [2]:

$$\text{Actual Half-Life (AHL)} = \frac{0.3\,\Delta T}{\text{Log}_{10}\,C_1/C_0}$$

ΔT = time interval (day) between C_0 and C_1
C_0 = original marker level
C_1 = level to which marker had fallen after ΔT days

The AFP levels obtained less than 3 days before or after the operation were used as the original marker (C_0). Serial serum AFP evels were followed after the operation at intervals of 4 days to 3 months. In many patients, following surgical resection the marker fell to within normal limits before a second assay was performed and the AHL could not be assessed. Patients with abnormal liver or renal function were excluded from the study because of the possibility of abnormal degradation of AFP. There were 18 evaluable patients: 15 had malignant GCTs (endodermal sinus tumor 7, embryonal carcinoma 3, malignant teratoma 5), 2 had hepatoblastomas, and 1 had hepatocellular carcinoma. The mean age was 3.4 years (range 1 day–12.5 years). The follow-up period ranged from 10 to 86 months. We used the International Histologic Classification of Tumors of the World Health Organization [7].

The patients were divided into group 1, who had complete resection of the tumor and no evidence of recurrence during follow-up, and group 2, who had residual disease after the operation or recurrence during follow-up. We postulated that recurrence of disease (residual tumor after surgical resection) could be determined by calculating the AHL of AFP. To test this hypothesis, the AHL of AFP for both groups was compared using the Kruskal–Wallis test. A P value of less than 0.05 was considered significant.

Results

Patient characteristics are summarized in Table 1. There were 13 patients in group 1; their serum AFP levels fell after surgery and remained normal during the follow-up period. In all 5 patients in group 2 who had incomplete resection or developed recurrent disease, the serum AFP did not decrease to normal after the operation and began to rise slowly again. In group 1 the AHL of AFP was 4.0 ± 0.9 days, in group 2, 24.8 ± 20 days. The AHL of AFP in group 2 was significantly longer than that in group 1 ($P = 0.0026$).

On serial determinations, an increasing half-life calculation preceded both a rise in serum AFP and clinical tumor recurrence by 2 to 7 weeks. In case 17, a left hepatic lobectomy was performed due to hepatocellular carcinoma. The resection margin was free of tumor and there appeared to be no residual tumor after the operation. However, the serum AFP initially decreased slowly and then began to increase by 7 weeks postoperatively. Follow-up magnetic resonance imaging of the abdomen showed multiple intrahepatic metastases (Fig. 1). Despite aggressive chemotherapy (5-fluorouracil, adriamycin, vincristine) at the time of clinical recurrence, the patient died of her disease 10 months after the operation. The retrospectively calculated AHL of AFP on the 8th postoperative day was increased (9.3 days), suggesting the presence of residual tumor after resection (Fig. 2).

Table 1 Summary of patient data (*EST* endodermal sinus tumor, *EMB* embryonal carcinoma, *TRT* malignant teratoma, *HPB* hepatoblastoma, *HCC* hepatocellular carcinoma, *AHL* actual half-life of alpha-fetoprotein)

Case no.	Age (years)	Sex	Tumor	Group	AHL (days)	Follow-up (months)
1	0.8	m	EST	1	3.17	36
2	3.7	f	EST	1	3.45	60
3	0.6	m	EST	1	3.08	43
4	1.5	m	EST	1	4.13	36
5	10.1	f	EST	2	13.06	31
6	1.1	m	EMB	1	4.25	44
7	3.9	m	EMB	1	4.22	30
8	0.8	f	EST	1	3.58	37
9	0.7	f	EST	2	75.42	15
10	0.7	m	EMB	1	3.61	86
11	0.3	m	TRT	1	4.2	36
12	12.4	f	TRT	2	5.74	76
13	0	m	TRT	1	9.79	38
14	12.5	m	TRT	2	20.53	13
15	0.9	m	TRT	1	4.81	27
16	0.8	m	HPB	1	4.99	23
17	6	f	HCC	2	9.31	10
18	4	f	HPB	1	3.29	17

Discussion

Kohn proposed that the clearance rate of a serum tumor marker after treatment could have prognostic significance [2]. It is reasonable to apply this concept to patients who have recently undergone curative resection, because if all tumor-marker-producing tissue has been removed, the tumor marker should decrease at or near the theoretical rates. Our results support Kohńs concept and also suggest that the AHL of AFP after resection becomes prolonged even before the rise in serum AFP and clinical tumor recurrence (Fig. 2). In many animal models, earlier treatment of preclinical disease yields better results because of the lower total number of tumor cells and tumor kinetic conditions favoring a response to therapy [8].

Although there was no "false-normal half-life" in our study, previous reports have described false-negative findings in the AHL of serum tumor markers in malignant GCTs [4, 9]. AFP is produced from embryonal carcinoma or endodermal-sinus tumors in malignant GCTs [3]. Malignant GCTs are heterogeneous and show changes in histology secondary to variable rates of growth or responses to therapy by different tumor elements. Thus, all AFP-producing tissue can be resected, but tumor tissue negative for AFP might remain. Another explanation for a normal half-life in recurrence is that the amount of marker produced by any residual tumor might initially be too small to affect the metabolic decay rate. Thus, an abnormal postoperative half-life has predictive value, whereas a normal half-life may not.

There was a false-positive result (9.79 days) in a neonate in our series (case 13). The half-life of AFP is normally 4–6 days [1], but in low-birth-weight infants it is prolonged for up to 7.5 days [5]. Further, in newborn

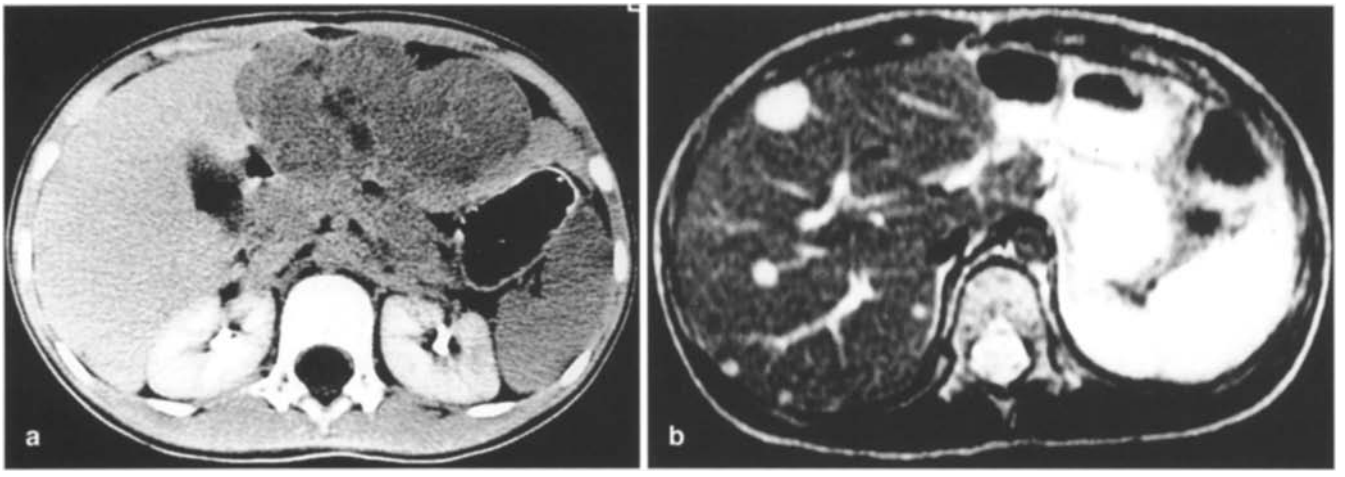

Fig. 1a Preoperative abdominal CT scan (case 17) shows huge, lobulated, solid mass in left lobe of liver. **b** Abdominal MRI shows multiple round nodules on remaining portion of liver

infants the normal level of AFP is approximately 20,000 to 100,000 IU/ml at birth [6]; adult values are reached after about the 10th month of life [12]. Hence, in the newborn up to 10 months of age, the treatment decision based on simple calculation needs to be approached with much greater caution.

The applicability of the half-life concept for patients undergoing chemotherapy is less obvious. In theory, effective chemotherapy can stop marker synthesis before it kills the cells, resulting in reduced marker production before tumor regression becomes evident clinically. In many patients marker levels increase abruptly after the first dose of chemotherapy, possibly as a result of release of markers by dead or dying cells. This increase is referred to as the release phenomenon, which usually disappears after 5 days [10]. Therefore, Lange et al. [4] recommended that the first marker level used in the calculation should be the first level determined at least 5 days after starting chemotherapy.

Serum tumor marker levels are continuously elevated until the growing tumor is removed by surgery. Therefore, the first marker level (C_0) used in calculation should be one determined immediately before or after surgical resection. A precipitous drop in half-life often occurs during lymphadenectomy of germ-cell tumors, which has not been fully explained, but may be dilutional if multiple blood transfusions are required [4]. In general, in the absence of postoperative complications, the corticoid-withdrawal phase starts 3 to 6 days after the major operation, characterized by spontaneous fluid homeostasis [11]. Thus, we believe that the ideal first follow-up marker level (C_1) for calculation should be obtained at least 3 days after surgery. We also recommend that after curative surgical resection all patients should be monitored with weekly assays for half-life calculation until the serum tumor marker becomes normal.

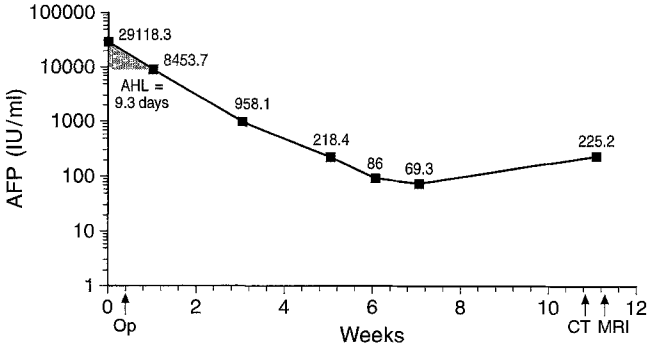

Fig. 2 Alpha-fetoprotein (AFP) levels of case 17. Serum AFP level decreased slowly and began to increase 7 weeks after the operation. Retrospectively calculated actual half-life (AHL) on 8th postoperative day was abnormally increased (9.3 days)

Because the rate of fall of serum levels of tumor markers may be influenced by physiological factors such as protein metabolism or renal clearance, patients with abnormal liver or renal function were excluded from the present study. AFP is metabolized in the liver, so that ideal follow-up of AFP requires normal hepatic function. However, major hepatic resections were performed in 3 of our patients whose hepatic function rapidly normalized after the operation. Two patients had normal AHL and had no recurrence during follow-up. In case 17 the tumor did recur, and the retrospectively calculated AHL was prolonged, which predicted a future recurrence of the disease (Fig. 2). We propose that a half-life assay of AFP might also be useful for follow-up of AFP-producing hepatic malignancies after major hepatic resection in children who do not have any severe hepatic dysfunction.

An important result of this study is the demonstration that an increasing AHL precedes both a rise in serum AFP and clinical tumor recurrence. It will clearly be advantageous to detect residual tumor after surgical resection by calculation of the AHL of AFP earlier so that alternative therapy can be employed. Further prospective studies are needed to determine if such early treatment based on half-life calculation does yield improved therapeutic results in AFP-producing malignant tumors in children.

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