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Variations in Normal Serum Alpha-Fetoprotein (AFP) Levels in Patients with Testicular Cancer on Surveillance

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Summary

Background: The aim of this study was to assess fluctuations in normal serum alpha-fetoprotein (AFP) levels in patients with germ cell cancer. Marked variations occur after serum AFP levels normalize, creating anxiety among patients and physicians during surveillance.

Patients and Methods: We conducted a retrospective review of patients with germ cell tumors in clinical remission, who had normal AFP levels and were followed at our center from 1991 to 2009. 72 patients, with a median follow-up of 50 months, were identified.

Results: Of the 72 patients, 57 (79%) had a non-seminomatous germ cell histology, and 15 (21%) had seminomas. Seminomas were included as controls as serum AFP levels do not increase in this group. 68 patients underwent orchiectomy, and 50 patients received systemic chemotherapy. The majority of patients (93%) demonstrated fluctuations in serum AFP. There was no difference in the mean AFP values between patients with seminoma (2.95 ng/ml) and those with non-seminomatous germ cell tumors (3.3 ng/ml) (standard deviation 1.01 ng/ml).

Conclusion: Marked variations occur after serum AFP levels normalize in patients undergoing surveillance. Fluctuating AFP levels within normal limits did not result in relapse in our cohort of patients with extended follow-up.

Zusammenfassung

Ziel dieser Studie war es, Schwankungen im normalen Alpha-Fetoprotein (AFP)-Serumspiegel bei Patienten mit Keimzelltumoren zu bewerten. Nach Normalisierung des AFP-Serumspiegels können starke Abweichungen auftreten, was sowohl für Patienten als auch für Ärzte besorgniserregend sein kann.

Patienten mit Keimzelltumoren in klinischer Remission und mit einem normalen AFP-Spiegel, die in unserer Institution von 1991 bis 2009 überwacht wurden, wurden retrospektiv analysiert. 72 Patienten mit einem mittleren Follow-Up von 50 Monaten wurden identifiziert.

Von den 72 Patienten hatten 57 (79%) eine nicht-seminomatöse Keimzellhistologie; 15 (21%) Patienten hatten ein Seminom. Seminome wurden als Kontrollen in die Studie aufgenommen, da

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der AFP-Serumspiegel in dieser Patientengruppe nicht ansteigt. Bei 68 Patienten wurde eine Orchiektomie durchgeführt, und 50 Patienten wurden mit systemischer Chemotherapie behandelt. Die Mehrzahl der Patienten (93%) zeigte Schwankungen im AFP-Serumspiegel. Zwischen Patienten mit Seminomen bzw. nicht-seminomatösen Keimzelltumoren bestanden keine Unterschiede im mittleren AFP-Serumspiegel (2,95 bzw. 3,3 ng/ml; Normalabweichung 1,01 ng/ml).

Während des Follow-Ups können nach Normalisierung des AFP-Serumspiegels starke Abweichungen auftreten. Schwankungen im AFP-Spiegel innerhalb des Normalbereichs führten in unserer Kohorte mit verlängertem Follow-Up zu keinen Rezidiven.

Keywords

Serum AFP; Surveillance; Relapse; Chemotherapy; Serum-AFP; Beobachtung; Rezidiv; Chemotherapie

Introduction

Testicular cancer accounts for 1–2% of all neoplasms in men [1]. It is the most common malignancy in otherwise healthy men 20–35 years of age and has an annual incidence of approximately 4 per 100,000 [2]. Tumor markers such as alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β HCG) have an established role in the management of testicular cancer [3, 4]. They are used for diagnosis and prognosis, monitored during therapy, and are followed after completion of therapy for relapse [5].

Physiologically, AFP is mainly produced in the liver and the yolk sac of human fetuses more than 4 weeks old, with peak values of up to 4 mg/ml at 12–16 weeks of gestation [6, 7]. With a half life of 5 days, AFP levels fall within 8–12 months after birth to a very low concentration of < 10 ng/ml and persist at low levels throughout life [8, 9]. Normal adult levels remain at approximately 2–4 ng/ml [10]. AFP is produced in approximately two-thirds of the patients with germ cell tumors containing yolk sac elements (embryonal carcinomas and endodermal sinus tumors). 90% of patients with nonseminomatous germ cell tumors (NSGCT) at any stage of the disease have elevated serum levels for AFP, β HCG, or both before treatment. Seminoma tumors do not increase AFP levels and occasionally increase β HCG levels. Persistent marker elevation after chemotherapy indicates persistent disease and the need for further therapy [11]. Patients are followed quite rigorously with tumor markers, physical examination, and computed tomography (CT) scans for a period of 5 years after orchiectomy, retroperitoneal lymph node dissection (RPLND), or chemotherapy [12]. Most relapses occur within the first year, and relapses after 2 years are rare. These relapses are detected before clinical symptoms appear.

Fluctuations in serum AFP levels within the normal range occur in patients during this follow-up period, causing anxiety about relapse. Patients frequently question the significance of an increase in AFP within normal levels and whether it predicts for relapse. We seek to evaluate the variations and fluctuations in serum AFP levels after it normalizes that occur in patients during their follow-up surveillance period.

Patients and Methods

We conducted a retrospective review of all patients with germ cell tumors, who were in clinical remission (defined as normal scans and normal markers) and followed with surveillance. This includes patients who have had an orchiectomy alone, those with an RPLND, and those treated with chemotherapy in addition to orchiectomy. All patients had AFP levels drawn at the Stanford University Cancer Center from 1991 to 2009. Patients were identified from pathology specimens after orchiectomy as well as from our electronic medical record database.

Patients were screened retrospectively for their initial serum AFP level, age, site of disease, date of diagnosis, tumor histology and grade, stage of disease, the availability of serial serum AFP level determinations, and disease status at last follow-up. Treatments including orchiectomy, surveillance, chemotherapy, retroperitoneal lymph node dissection, and radiation were documented. Stage of disease was based on the TNM Classification of Malignant Tumors as published in the AJCC Cancer Staging Manual.

Patient charts were reviewed for a complete history, physical examination, appropriate imaging studies (chest X-ray, CT, magnetic resonance imaging, and positron emission tomography), and serum AFP levels. Serum AFP levels were measured pre-operatively and during surveillance. The serum levels of AFP were determined using an AFP enzyme immunoassay (Siemens AFP ADVIA Centaur Immunoassay Systems, Siemens Deerfield, IL, USA) according to the manufacturer's instruction. All serum samples were analyzed in the same laboratory at Stanford Hospital. The upper limit of normal of serum AFP was 10 ng/ml at our institution.

To the patients that received systemic chemotherapy, a combination of a platinum agent, etoposide, and bleomycin was given every 3 weeks for a total of 3 or 4 cycles. Subsequent regimens included TIP (paclitaxel, ifosfamide, cisplatin) or VIP (etoposide, ifosfamide, cisplatin). Patients undergoing surveillance were followed according to National Comprehensive Cancer Network (NCCN) guidelines. Relapse was identified by abnormal clinical exam, rising tumor markers, or radiographic imaging.

From a total of 176 patients, 72 were considered eligible for the study based on the following criteria: i) no relapse and normal AFP levels (< 10 ng/ml); ii) histological documentation of germ cell cancer from orchiectomy specimens at our institution; iii) undergoing regular followup visits; iv) complete clinical and radiographic follow-up with serum AFP determinations and/or radiographic scans at regular intervals; v) clinical and radiographic determination of disease status at the time of last follow-up or recurrence.

We included patients with seminoma in our analysis to serve as a control group since elevations in AFP levels are not expected in this histology but are routinely obtained both at diagnosis and subsequent follow-up. We evaluated serum AFP levels for each patient from the time that the AFP level normalized to last follow-up. The study protocol was evaluated and approved by the Institutional Review Board at Stanford University.

Statistical Analysis

For each subject, the mean AFP level was calculated using every AFP measurement starting from the date when AFP reached a normal level or less, until the date of last contact, up to 10 years. Differences in group scores were assessed with unpaired t-tests, and effects were considered statistically significant with a p value < 0.05. All analyses were conducted with SAS 9.2 TS2M3 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 72 patients, 57 (79%) had a non-seminomatous germ cell histology and 15 (21%) had seminomas (table 1). 33% of patients were stage I, 6% were stage Is, 28% were stage II, and 33% were stage III. 68 patients underwent orchiectomy, and 50 patients received systemic chemotherapy. 4 patients had extragonadal primaries. 3 patients required a hematopoietic stem cell transplant. The mean age of patients at diagnosis was 30.6 years. Median follow-up was 52 months. Overall, each patient had an average of 12.76 samples (range 1–39) over 3.5 years (range 127–3,526 days). Figure 1 shows the trajectory of AFP scores for each individual patient. Almost all patients had fluctuations within the normal range during the follow-up period. Of the 57 patients with NSGCT, 1 had no fluctuation. The remaining 56 patients had significant variations, but none relapsed within the long follow-up period. Of the 15 patients with seminoma in whom AFP levels are not expected to rise, 13 patients demonstrated fluctuations in AFP levels and none relapsed (fig. 2). The mean AFP value across all samples was 3.18 ng/ml (range 0.80–10 ng/ml) with a standard deviation (SD) of 1.73 ng/ml. Furthermore, there was no evidence of a difference in the mean AFP values between patients with seminoma (2.95 ng/ml) and those with non-seminomatous germ cell tumors (3.36 ng/ml) ($p < 0.31$).

Discussion

Tumor markers are of central importance in the diagnosis, staging, risk assessment, and monitoring of patients with testicular cancer. Rising levels of AFP above normal indicate persistent germ cell tumor even in the absence of radiographic evidence of disease. Various malignancies rely on the use of tumor markers for early indications of disease activity in patients who achieve a complete clinical response after primary treatment. In ovarian cancer, different prognostic groupings exist within the commonly regarded normal CA-125 range, where the upper limit of normal is 35 U/ml. In a group of ovarian cancer patients in complete clinical remission, Santillan et al. [13] reported that progressive, low-level increase in serum CA-125 levels is strongly predictive of radiographic disease recurrence. The specific patterns of increase investigated were an absolute increase of 5 U/ml from nadir, an absolute increase of 10 U/ml from nadir, and doubling of the CA-125 nadir. In an updated analysis, patients with CA-125 levels in the range of < 10, 10–20, and 21–35 U/ml had a different risk of progression. The median progression-free survival of the 3 groups was 58, 45, and 37 months, respectively [14].

In our study, the majority of patients had a non-seminomatous histology and stage II or III disease. Most had an orchiectomy followed by a systemic chemotherapy regimen. 67 (93%) patients in our cohort had fluctuations in serum AFP within normal levels. Exploratory

visualization of the data did not show any evidence of a pattern in AFP. The mean AFP value across all samples was 3.18 ng/ml (range 0.80–10 ng/ml) with an SD of 1.73 ng/ml. Thus, variations within the normal range were very common, with a majority of patients having fluctuations in normal serum AFP levels. To our knowledge, this has never been reported previously.

Our study was limited due to its small sample size as well as selection bias. Given the long follow-up of the patients who have not relapsed, it is reassuring that variations of serum AFP within normal levels were common and did not indicate a relapse. The patients that were included for our review were those that had adequate laboratory data and were able to participate in regular clinic visits and testing for surveillance. We used patients with seminoma as a control group as we would not expect AFP values to be elevated in this histology even though laboratory testing is routinely performed in the clinical practice setting. Our retrospective review of patients with testicular cancer while on surveillance shows high fluctuations in the level of serum AFP once it has reached normal values. The pattern of fluctuation was not helpful in predicting relapse. Patients should be reassured that a majority does have fluctuations within normal values which do not necessarily result in a relapse.

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Fig. 1. Individual serum alpha-fetoprotein (AFP) levels. Range (min/max) and overall mean of serum AFP scores for 52 NSGCT patients (gray) and 15 seminoma patients (black).

Fig. 2. Mean serum alpha-fetoprotein (AFP). Schematic boxplots (with mean drawn as diamonds, whiskers extending 1.5 IQR and all outliers drawn as open circles) showing the distribution of AFP scores for 52 Patients with NSGCT and serum AFP scores for 15 patients with seminoma.

Table 1.

Patient characteristics

	Patients, %
Age, years	
0–20	8
20–30	44
30–40	29
40–50	19
Treatment	
Surveillance alone	17
Radiation	7
Chemotherapy	67
RPLND	35
Bone marrow transplant	6
Staging	
I	33
Is	6
II	28
III	33
Pathology	
NSGCT	79
Seminoma	21
Orchiectomy (right or left)	94
Extragenadal primaries	6

RPLND = Retroperitoneal lymph node dissection

NSGCT = non-seminomatous germ cell tumor.