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Serum Estradiol as a Tumour Marker for Non-seminomatous Germinal Cell Tumours (NSGCT) of the Testis

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Radioimmunoassay (RIA) determinations of serum alphafetoprotein (AFP), beta human chorionic gonadotropin (BHCG) and estradiol (E_2) levels have been made at various stages of the disease in 52 patients with testicular carcinoma. In non-seminomatous tumours of the testis, E_2 has been found to be a highly specific tumour marker, helping to reduce clinical staging error. Increases in serum E_2 levels have been observed in all patients with HCG-secreting tumours, but E_2 has indicated tumour recurrence alone in 4 patients with normal AFP and BHCG levels. Gynecomastia, always accompanied by a rise in serum E_2 and BHCG levels has been a bad prognostic sign. E_2 had no significance as a marker in seminomatous tumours.

Introduction

A unique feature of testicular tumours is their secretion of tumour markers like AFP and BHCG, which indicate the presence of malignant elements and tumour activity [1, 2]. Even in the absence of clinical findings to indicate metastatic activity, elevation of markers alone has been considered to be an indication of further therapy [3].

Although there are a lot of reports in the literature on high accuracy rates for AFP and BHCG, false-negative results reaching 38% have been obtained by various researchers [4]. It has been noted that more tumour-specific markers are needed for testicular tumours, because elevations of these markers can influence clinical decisions on further operative interventions and chemotherapy, which are not without complications [9].

To determine the false-negative and false-positive values for AFP, BHCG and E_2, we have made routine RIA determinations of these markers in 52 patients with testicular carcinoma during a follow-up period of 2 years and compared the results with various clinical findings.

Patients and methods

The records of 52 patients with testicular cancer treated in a 2-year period were reviewed. Patient age at diagnosis ranged from 15 to 50 years (average age 30.4). Patients were followed up for 2–24 months, the average follow-up duration was 18 months. The AFP, BHCG and E_2 assays were done with standard radio-

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immunoassay techniques performed before and after orchiectomy, retroperitoneal lymphadenectomy and chemotherapy and during subsequent follow-up at 1–3-month intervals.

As part of the evaluation, all patients had lung tomography, excretory urography and abdominal ultrasonography performed with interval abdominal CAT scanning. Of the 52 patients 11 had seminomatous tumours. Using the Walter-Reed pathologic staging, 17 patients had Stage I, 23 Stage II and 12 Stage III disease [8]. Retroperitoneal lymphadenectomy (RPLD) was carried out bilaterally. A combination of cis-platin, vinblastine and bleomycin was used for chemotherapy, with epotoside administered for bulky disease.

Results

Of the 52 patients, 11 were seen before orchiectomy, presenting with testicular masses. Before orchiectomy there was an elevation of AFP in 5, BHCG in 6 and E_2 in 8 patients. Three patients had seminomatous tumours, with markers being negative before and after orchiectomy. In this group 7 patients were later staged as having Stage II–III non-seminomatous tumours; AFP was elevated in 5, BHCG in 5 and E_2 in 7, before orchiectomy. After orchiectomy AFP levels were normal in 3, BHCG in 2 and E_2 was elevated in all patients. Before orchiectomy false-negative values were 28.5% for AFP and BHCG each and 0% for E_2.

After orchiectomy tumour marker levels were obtained in a total of 40 patients, 33 of them with non-seminoma ous tumours. In 14 patients with Stage I NSGCT, false-positive results occurredt in 35.7% for AFP, 7.1% for BHCG and 10% for E_2. In 19 patients with Stage II–III NSGCT, false-negative results reached 26.3% for AFP, 47.6% for BHCG and 20% for E_2. In the Stage II–III NSGCT group an elevation of AFP or BHCG or both was noted in 80% of the patients. When E_2 elevations were combined with AFP and BHCG, at least one of the markers was elevated in 95% of these patients. E_2 elevation was noted in all patients with HCG-secreting tumours.

In 21 patients bilateral retroperitoneal lymphadenectomy (RPLD) was performed. After RPLD, 11 patients were evaluated as having Stage I tumours, with no further therapy administered; 10 had metastatic spread on RPLD and received chemotherapy. After RPLD, no false-positive values have been noted for AFP and BHCG. False-positive E_2 elevation was noted in one patient (12.5%) with Stage I disease, which later returned to normal levels during follow-up.

To determine the prognostic values of tumour markers, 14 patients who had marker elevations prior to RPLD were compared to 7 patients who had normal markers before RPLD. Of the 14 patients with elevated markers, 4 proceeded to Stage III; however, no disease progression was noted in the group with normal markers.

Forty-three patients were followed up after therapy and AFP, BHCG, E_2 levels were determined. With E_2, 10.7% false-positive and 20% false-negative results were obtained. False-negative values were 9.3% for AFP and 11.6% for

BHCG. No false-positive values have been noted with AFP and BHCG. In 4 patients with disease recurrence, only E_2 levels were elevated, whereas AFP and BHCG remained within the normal range. Eight patients had disease recurrence and along with it AFP was elevated in 50%, BHCG in 37.5% and E_2 in 80% of them. However, when combined, at least one of these markers was elevated in 87.5% of the patients.

Gynecomastia was noted in 6 patients (11.5%) and serum E_2 levels were elevated in all of them along with serum BHCG. AFP was increased in only 60%. Four of these patients had choriocarcinoma. Three patients (50%) died of metastatic disease, on average 2 months after initial diagnosis. This group had the worst prognosis in our study.

Discussion

Testicular tumour markers have been found to be valuable and highly specific in the diagnosis and follow-up of patients with testicular carcinoma. Using these markers, information can be gained regarding the efficacy of therapy, metastatic activity and recurrence during follow-up [1, 2, 3]. Routine utilization of tumour markers can influence therapeutic decisions in clinical practice. At the time of initial elevation of these markers, chances of obtaining a good response to therapy are highest, because tumour-load will be minimum at this stage [1].

It has been noted that with AFP and BHCG determinations, clinical staging can be made more accurately [3, 8]. Scardino and Cox [3] have noted an elevation of at least one of these markers in 91% of their patients, observing no false-positive results. But Skinner and Scardino [4] have reported a false-negative value of 38% with these two markers in Stage I–II NSGCT. An obvious conclusion derived from these findings is that more specific markers are needed considering the decisions based on marker levels.

In our study determinations before orchiectomy have revealed no false-negative results for E_2 in 7 patients with Stage II–III NSGCT, whereas it was 28.5% for both AFP and BHCG. It has been noted by Scardino and Cox [3] that with AFP and BHCG determinations clinical staging error was reduced from 35% to 14% before RPLD. In our study staging error for NSGCT was 28.5% with both AFP and BHCG, but with the combination of E_2 it has been reduced to 11.4%. Also in Stage II–III NSGCT, AFP and/or BHCG levels were high in 80% and with the addition of E_2, a marker elevation was noted in 95% of the cases. Thus, we have concluded that E_2 determination is a good adjunct to AFP and BHCG, being highly specific and reducing staging errors.

In all patients with HCG-secreting tumours there was a simultaneous increase in serum E_2 levels, but we have not seen a single case where serum E_2 levels were normal with BHCG elevations. E_2 was elevated in 70% of the patients with elevated AFP levels.

Our results are in accordance with those of Aiginger and Kolbe [5] who observed elevated E_2 levels in patients with HCG-secreting tumours. Also the fact

that E_2 levels were not so much elevated in AFP-secreting tumours as those of BHCG-secreting tumours has been explained by the findings of Kirschner and Cohen [6] who reported that AFP binds E_2 strongly within the tumour mass, thus decreasing serum levels of estradiol.

Out of 14 patients with elevated markers before RPLD 4 have proceeded to Stage III disease, whereas no progression to further stages has been noted in 7 patients with normal markers before RPLD. In a study to determine the prognostic value of tumour markers, Scardino and Cox [3] found an increased chance of disease recurrence in patients with elevated pre-RPLD markers, which supports our findings.

Gynecomastia was noted in 6 patients (11.5%) and all had significantly high E_2 and BHCG elevations. Three of them died within 2 months from metastatic choriocarcinoma. Gynecomastia displayed a bad prognostic sign in patients with testicular carcinoma, which has also been reported by Stepanas and Naguib [10]. Javadpour [7] observed gynecomastia in 7 (11%) of his 62 white patients, but has not commented on prognosis.

During follow-up after definitive therapy, independent elevations of E_2 were able to show disease recurrence in 4 cases with normal AFP and BHCG levels. During follow-up, 10.7% false-positive and 20% false-negative values have been obtained for E_2, which is a comparable result to that of White and Karian [2] who reported a 20% false-negative value for AFP and BHCG combined.

In the light of our findings we have concluded that serum estradiol can be used as a reliable and highly specific marker in non-seminomatous germinal cell tumours of the testis. We have not found it to be a useful marker for seminomatous tumours.

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