EVALUATION OF TUMOUR MARKERS IN OUR CLINICAL ENVIRONMENT

AMJAD AZIZ KHAN, SHER MUHAMMAD KHAN,
GUL NAWAB AND IFTIKHAR AHMAD

Institute of Radiotherapy and Nuclear Medicine, Peshawar.

SUMMARY

Evaluation of tumour markers was done in 242 patients of various malignancies at different stages and phases of treatment. This evaluations was done in randomly selected cases. Five tumour markers were evaluated namely, Carcinoembryonic Antigen (CEA), Alpha Feto Protein (AFP), CA 125, Prostatic Acid Phosphatase (PAP) and Human Chorionic Gonadotrophin (HCG). Titres of PAP were raised in patients with carcinoma of prostate while all other tumour markers showed varied positive results ranging from 30-50%. Testicular tumours showed comparatively higher titres Sensitivity and specificity varied with other tumour marker in different malignancies.

INTRODUCTION

Cancer is a major cause of morbidity and mortality throughout the world. The epidemiology of malignant diseases is still poorly understood. A tumour of 1 cubic centimeter contains one billion cancer cells. Despite an early diagnosis and surgical removal, the patient may have undetected metastases. In patients with advanced stages of disease and particularly with intra-abdominal malignancies, it is often difficult to assess disease progression and response to the treatment. The integration of conventional radiology with ultrasound, radioisotope techniques, CT scanning and eventually nuclear magnetic resonance is an increasingly interesting and challenging area. Acquainted with precise diagnosis and definition of tumour extent, the clinician must then decide on therapy. Should it be surgery, radiotherapy or chemotherapy or more of these techniques combined? Another step is to monitor treatment. A method is sought, which could provide information about tumour activity, response to treatment, disease free state and recurrence at an earlier stage.

MATERIAL AND METHODS

Patient Selection

For the determination of various tumour markers, i.e. CEA, AFP, CA 125, PAP and Beta HCG in different malignancies, blood samples were collected from patients referred to the Institute of Radiotherapy and Nuclear Medicine, Peshawar, for radiotherapy/chemotherapy. These samples were collected at various phases of treatment, i.e. before starting treatment, during treatment, and after completion of therapy. These samples were analysed by Radio immunoassay techniques.

Quality Control

Quality Control measures were strictly followed to ensure that the results obtained were reliable. Policy of quality control includes both the internal and external quality control.

RESULTS

Carcinoembryonic Antigen (CEA)

Our study included 66 cases with various malignancies at different stages and phases of treatment. In roughly half of these we found abnormal CEA values; no

significant correlation was seen with the staging or the phase of treatment. The titres of CEA were found abnormally raised of G.I. malignancies. Range was 4.4-60 ng/ml (Table-1).

Alpha Fetoprotein (AFP)

Table-2 depicts the results of alpha fetoprotein (AFP) in 44 patients with various stages of malignancies and phase of treatment. It included 8 patients with Ca ovary, 8 Ca testes, 3 Ca breast, 3 Ca Oesophagus, 3 cirrhosis while 8 cases had Ca liver for which it is mainly indicated. In our study of 44 cases of various carcinomas and cirrhosis, an expected pattern was encountered. Two of the six cases of untreated testicular carcinoma showed markedly elevated values and they both belonged to stage IV. Stage I and II cases did not show any abnormal AFP

TABLE – 1

DATA FOR CEA (NORMAL RANGE < 4 ng/ml)

No	Tumour	Stage	Phase of Therapy		
			Pre	Dur	Post
1	Ca Breast (9)	IV		31.2 (2)	
		II		8.41 (3)	
		I	1.6 (1)	0.76 (2)	17.3 (1)
2	Ca Ovary (5)	IV	3.17 (1)	1.80 (1)	
		III	3.1 (2)		0.74 (1)
		II			0.74 (1)
3	Ca Uterus (2)	I		3.65 (2)	
4	Ca Cervix (2)	III		>60 (1)	
		II			21.7 (1)
5	Ca Testis (4)	IV			0.8 (1)
		II	4.4 (1)		1.4 (1)
		I		1.9 (1)	
6	Ca Prostate (1)	III			8.1 (1)
7	Ca U. Bladder (4)	III		11.81 (1)	
		II			1.95 (3)
8	Ca Oesophagus (10)	IV	> 60 (1)		
		III	> 60 (1)		
		II	2.97 (1)	6.06 (2)	
		I	9.8 (1)	5.7 (2)	
9	Ca Stomach (3)	II		3.93 (3)	
10	Ca Pancreas (1)				0.8 (1)

TABLE – 2

DATA FOR AFP (NORMAL RANGE 0–20 ng/ml)

No	Tumour	Stage	Phase of Therapy		
			Pre	Dur	Post
1	Ca Breast (3)	III		0.0 (1)	
		II	0.0 (1)		0.0 (1)
2	Ca Ovary (8)	IV	0.0 (1)		
		III	0.0 (2)	0.48 (2)	0.19(1)
		II	0.0 (1)	0.0 (1)	
3	Ca Vagina (1)	II	0.0 (1)		
4	Ca Cervix (1)	III	0.0 (1)		
5	Ca Testis (8)	IV	67.6 (4)		
		II	0.46 (1)	0.0 (1)	
		I	3.42 (1)		0.0 (1)
6	Ca U. Bladder (2)	II		2.91 (1)	2.03 (1)
7	Ca Oesophagus (3)	III		0.0 (1)	
		II		0.0 (1)	0.0 (1)
8	Ca Stomach (1)	II		0.0 (1)	
9	Ca Pancreas (1)	II		0.0 (1)	
10	Ca Rectum (1)	III		0.11 (1)	
11	Ca Liver (8)	IV	135.25 (3)		
		III	35.88 (2)		
		II	75.17 (3)		
12	Ca Gall Bladder (1)	III	0.0 (1)		
13	Ca Lung (2)	IV		0.0 (1)	
		II		0.0 (1)	

values. Out of eight Ca liver, five of the untreated cases showed high AFP values. A cirrhotic case also showed high AFP value. The titres were found abnormally raised in 13 cases with a range of 35.88-200 ng/ml.

CA 125

CA 125 was performed in 36 patients (Table–3) which included 6 controls, 6 carcinoma cervix, 4 carcinoma uterus, 11 carcinoma ovary and 1 carcinoma breast. Another groups of 8 individuals was also included who had various malignancies. Out of these 30 patients we found abnormally raised CA 125 levels in 15 cases. In cases of carcinoma of ovary, 9 out of 12 cases showed abnormally high values; out of these, 7 were untreated cases belonging to

TABLE – 3

DATA FOR CA 125 (NORMAL RANGE 0–35 units/ml)

No	Diagnosis	Stage	Phase of Therapy		
			Pre	Dur	Post
1	Ca Breast (1)	III		11.74 (1)	
2	Ca Ovary (12)	IV	568.82 (4)	159.0 (1)	
		III	201.09 (4)	21.37 (1)	
		II		55.8 (1)	0.0 (1)
3	Ca Uterus (4)	IV	22.49 (1)		
		II	0.0 (1)		
		I		0.0 (2)	
4	Ca Cervix (6)	III	13.98 (1)	379.3 (1)	
		II	30.71 (1)	29.8 (1)	42.29 (1)
		I		106.0 (1)	
5	Miscellaneous				
—	Ca Oesophagus (1)	II	18.01 (1)	234.2 (1)	
—	Ca Stomach (1)	II	37.73 (10		
—	Ca Vulva (3)	II		22.28 (2)	
		I	34.31 (1)		
—	Ca Vagina (1)	I			0.0 (1)
—	Choriocarcinoma (1)	III	57.79 (1)		
6	Control Group		24.61 (6)		

stage III and IV while 2 cases were in treatment - one in stage II and another in stage IV. One fully treated case showed normal CA 125 value. Six cases of carcinoma cervix were evaluated, 2 showed high CA 125 values while one was borderline abnormal. In these cases the range of abnormal levels was 37.73-568.82 u/ml.

Prostatic Acid Phosphatase (PAP)

Table-4 shows results of PAP in 23 patients. Amongst these, 8 patients had Ca prostate, 6 Ca urinary bladder, 1 each had Ca testis, pancreas, and breast. 6 patient were included in the group of miscellaneous malignancies.

Titres of PAP were found abnormally raised in 7 patients with a range of 9.72-17.14 ng/ml. These abnormally raised levels were found in patients with carcinoma prostate only while other patients did not show any significant levels of PAP.

TABLE – 4

DATA FOR PAP 125 (NORMAL RANGE 2.2–5 ng./ml)

No	Diagnosis	Stage	Phase of Therapy		
			Pre	Dur	Post
1	Ca Breast (1)	IV		0.0 (1)	
2	Ca Testis (1)	IV			0.0 (1)
3	Ca Prostate (8)	IV	15.71 (2)		17.14 (2)
		III	0.41 (1)	1.42 (1)	
		II	14.2 (1)	9.72 (2)	3.3 (1)
		I		1.0 (1)	
4	Ca U. Bladder (6)	III	1.75 (1)		
		II		0.21 (2)	0.25 (3)
5	Ca Pancreas (1)	II		0.0 (1)	
6	Miscellaneous				
—	Neuroendocrine (1)	II		0.0 (1)	
—	Osteosarcoma (1)	I		0.0 (1)	
—	A.M.L. (1)	II	3.1 (1)		
—	Ca Thyroid (1)	I			0.23 (1)
—	Ca Maxilla (1)	III		0.0 (1)	
—	Basal Cell Ca (1)	I			0.0 (1)

Human Chorionic Gonadotrophin (HCG)

Table-5 depict HCG levels in 73 patients at various stages and phases of treatment. Amongst these patients, 15 had Ca breast, 13 Ca bladder, 12 Ca testis, 9 Ca ovary, 4 Ca rectum, 3 Ca cervix, 2 Ca uterus and 2 had Ca stomach. One group contained patients with miscellaneous malignancies. Forty patients had raised levels with a mean range of 4.3-200 mIU/ml. High titers were seen in 8 of the 12 cases of carcinoma testes evaluated. It was interesting to see that 4 of these cases were on active treatment while 2 were in the post treatment phase. In cases of carcinoma urinary bladder, 7 of the 13 cases showed high HCG levels; 3 were untreated cases, 2 were on treatment while interestingly 5 of the 7 untreated cases showed abnormal HCG values.

DISCUSSION

Carcinoembryonic Antigen

CEA as a marker has probably received most attention and has been shown to be raised in gastrointestinal cancers, colonic cancers, tumours of the liver, breast carcinomas etc. However, CEA values are also affected by other non-tumour conditions ranging form cirrhosis and hepatitis to an ureteric obstruction and even in heavy smokers.[1] As a screening test it has limited value and it has been used more in assessing response to treatment and selecting cases for second-look surgeries and re-evaluation.[2]

TABLE – 5

DATA FOR HCG (NORMAL RANGE < 4 mIU/ml)

No	Diagnosis	Stage	Phase of Therapy		
			Pre	Dur	Post
1	Ca Breast (15)	IV	8.47(1)	11.69 (1)	17.3 (2)
		III	2.78 (2)	0.63 (3)	0.0 (1)
		II		7.23(1)	0.0 (1)
		I	0.76 (1)	16.4 (1)	1.1 (1)
2	Ca Ovary (9)	IV	2.66(2)	14.61 (1)	2.6(1)
		III		5.42 (1)	10.28 (1)
		II			8.4 (1)
		I	4.48 (2)		
3	Ca Uterus (2)			3.55 (2)	
4	Ca Cervix (3)	II	3.46 (1)	6.0 (1)	
		I			1.1 (1)
5	Ca Vagina (1)	II			3.7 (1)
6	Ca Testis (12)	IV		200.0(1)	200.0 (1)
		III	10.54 (1)	27.26 (1)	200.0 (1)
		II	101.0 (2)	4.3 (2)	
		I	2.92 (1)	9.91 (1)	
7	Ca Prostate (1)	IV		0.0 (1)	
8	Ca U. Bladder (13)	III		1.77 (1)	2.41 (4)
		II	7.9 (2)	11.34 (2)	5.49 (3)
		I	4.32 (1)		
9	Ca Oesophagus (4)	III	2.03 (1)	4.38 (2)	
		I	84.72 (1)		
10	Ca Stomach (2)	I	1.62 (1)		1.8 (1)
11	Ca Pancreas (1)	II		2.1 (1)	
12	Ca Colon (1)	I	1.53 (1)		
13	Ca Rectum (4)	III		5.3 (1)	
		II			1.46 (2)
		I		4.32 (1)	
14	Ca Liver (1)	II		40.33 (1)	
15	Ca Lung (1)	II		4.65 (1)	
16	Miscellaneous				
—	Chondrosarcoma (1)	I	0.0 (1)		
—	Sarcoma Chest (1)	I	0.0 (1)		
—	Renal Cell Ca (1)	III			17.94 (1)

Our study included 66 cases of a variety of carcinomas in various stages and phases of treatment and in roughly half of these we found abnormal CEA values; no significant correlation was seen with the staging or the phase of treatment. (We feel that this is reflected on our patient population specially as only single samples were taken at random points along the course of the disease and serial follow up was not done). This was expected in view of the wide ranging sensitivity of the marker to a variety of conditions and we failed to assess the real utility of this marker, i.e. to monitor patients serially and to evaluate their response to treatment or relapse of disease.[3,4]

Alphafetoprotein (AFP)

The last two decades have seen a number of studies demonstrating the association of significantly elevated serum AFP concentrations in a variety of conditions including hepatocellular carcinomas, testicular and ovarian teratomas, various foetal abnormalities and other varied conditions like cirrhosis,hepatitis, tyrosinosis and ataxia talangectasia. In our study of 44 cases of various carcinomas and cirrhosis, and expected pattern was encountered. Two of the six cases of untreated testicular carcinoma showed markedly elevated values and they both belonged to stage IV. Stage I and II cases did not show any abnormal AFP values. Eight cases of carcinoma liver were studied and five of the untreated cases showed high AFP values. A cirrhotic case also showed high AFP values. Our pattern is in accordance with that of other workers.[5,6,7] We feel that although AFP is not highly specific for any particular malignancy, its role in the staging of testicular teratomas and hepatocellular carcinomas and in the monitoring of the disease state cannot be under-estimated. It would be worthwhile to note that abnormal values were of cases in the pretreatment phase and their follow up estimations would certainly be useful for assessing prognosis and evaluating response to therapy.

CA 125

CA 125 promises to be a clinically useful marker in monitoring response to treatment in majority of patients with eptathelial carcinoma and since its false positivity is fairly low (less than 1% in healthy controls, in cases of endometritis etc.) it becomes all the more specific. Our study included six controls and 86 patients.

In cases of carcinoma of ovary, 9 out of 12 cases showed, abnormally high values; out of these 7 were untreated cases belonging to stage III and IV while 2 cases were in treatment-one in stage II and another in stage IV. One fully treated case showed normal CA 125 value. We generally found good correlation of high CA 125 values with the extent of the spread of the disease. A significant correlation has also been found between CA 125 levels and the regression, stability, or progression of epithelial ovarian carcinomas.[8,9]

Six cases of carcinoma cervix were evaluated, 2 showed high CA 125 values while one was borderline abnormal. In cases of cervical adenocarcinomas CA 125 is reflective of degree of invasiveness but it is only raised in 30-40% of such cases.[10]

Our study thus establish the high specificity of CA 125 in carcinoma ovary and to a lesser extent in carcinoma cervix.

Prostatic Acid Phosphatase (PAP)

PAP, a major constituent of the seminal vesical and present in the prostatic tissue including adenoma and carcinoma, is normally present in the serum at very low levels. It is specifically a reflection of prostatic status and gets elevated in carcinoma, infarction and transiently after manipulation of the other prostate. Although its utility as a screening test for intracapsular carcinomas is rather doubtful, it is certainly of great use in monitoring the stage and response to treatment of prostatic malignancies.[11] We studied 28 cases of various malignancies and found no abnor-

mal high values in any types of malignancy except carcinoma of prostate.

Human Chorionic Gonadotrophin (HCG)

HCG, reflective of trophoblastic activity in the body, is raised in pregnancy, hydatidiform mole, choriocarcinoma, testicular carcinomas and some other neoplasms of trophoblastic and non trophobaltic origin. It has also been reported to be increased in cases of carcinoma of the urinary bladder. Its role in cases of hydatidiform mole and in monitoring radiotherapy for choriocarcinoma is well established. However, in cases of seminomatous and non seminomatous testicular tumours, the role of HCG is still not very clear. In our study of 73 cases of various types of carcinomas a spectrum of abnormalities was noted. High titers were seen in 8 of the 12 cases of carcinoma testes evaluated. It was interesting to see that 4 of these cases were on active treatment while 2 were in the post treatment phase. In cases of carcinoma urinary bladder, 7 of the 13 cases showed high HCG levels; 3 were untreated cases, 2 were on treatment while interestingly 5 of the 7 untreated cases showed abnormal HCG values. This could be used for monitoring response to treatment.

CONCLUSION

We have been able to establish these 5 tumour markers in our centre. RIA and quality control were looked into and attempts were made to include as varied a cancer population as possible so as to establish and communicate to the clinician the utility and the role of these markers in the staging, selection of treatment protocol and in the evaluation of post-treated cases coming for routine check-up or presenting with clinical evidence of reactivation of the disease process.

REFERENCES

1. Lowenstein MS, Zamcheck N. Carcinoembryonic antigen levels in benign gastrointestinal disease states. Cancer 1978; 42: 1412.
2. Stabb HJ, Andre FA, et al. Prognostic value of preoperative serum CEA level compared to clinical staging Br Jour Cancer 1982; 44: 652.
3. Lokich JJ, Zamcheck N, Lowenstein MS. Sequential carcinoembryonic antigen levels in the therapy of metastatic breast cancer. Ann Int Med 1981; 89: 902.
4. Skarin AT, Delwiebe R, Zamcheck N, et al. CEA antigen clinical correlation with chemotherapy for metastatic GIT cancer. Cancer, 1974; 33: 1239.
5. Abelev GI, Assecritova IV. Perova Intjoul Cancer, 1967; 2: 551.
6. Abelev GI. Production of embryonal serum alpha-globulin by hepatoma: Review of experimental and clinical data. Cancer Res 1967: 24: 1344.
7. Nishi S. Isolation and characterization of a human fetal alpha globulin from the sera of fetuses and a hepatoma patient. Cancer Res 1970; 30: 2507.
8. Bast RC, Knapp RC. The immunobiology of ovarian carcinoma. Gyn Oncol 1983; 187: 226.
9. Bast RC Jr, Klung RST, John E, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithetial ovarina cancer. New Eng. Jour Med 1983; 309: 883.
10. Nanbu Y, Fuji S, Konish I, et al. Immunohistochemical localizatio of CA 125, CEA, CA 19-9 in normal and neoplastic cells of uterine cervix. Cancer 1988; 62: 2580.
11. Cooper JT, Foti A, Herschman H. Combined serum and bone marrow radioimmunoassay for prostatic acid phosphatate. Jour Urol 1979; 122: 498.