Tumor Markers in Patients Undergoing Hemodialysis and Kidney Transplantation

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ABSTRACT

Objective: To evaluate the effect of dialysis and kidney transplantation on serum levels of several tumor markers such as PSA, AFP, CA125, CA19-9, CA15-3, CEA and to compare with normal age matched controls.
Methods: Between September of 2000 and July of 2001, the following tumor markers: PSA, AFP, CA125, CA19-9, CA15-3 and CEA were measured by ELISA Method in 29 hemodialyzed patients (group A), in 30 successfully transplanted patients (group B) and in 30 normal volunteers who did not present any clinical symptoms or signs of neoplasia. **Results:** The serum level of CEA was above the cutoff limit in 6.7% of hemodialyzed patients (group A) but was in the normal range in transplanted and control groups. The level of CEA were significantly higher in hemodialyzed patients in comparison to other groups ($p<0.003$). Serum levels of AFP and PSA were not significantly different between the three groups ($p=0.595$ and $p=0.545$, respectively). Although serum level of CA 19-9 was elevated in 3.3% of hemodialyzed and control group the differences between the three groups were not significant ($p=0.507$). Serum level of CA 125 was elevated in 13.3% of group A, 13.8% of group B and 6.7% of control group ($p=0.347$). Serum level of CA15-3 was elevated in 13.3%, 6.9% of group A, B and control group, respectively and the differences were not significant ($p=0.156$).
Conclusion: Hemodialyzed and transplanted patients show a high false positive rate of CEA, CA125 and CA15-3 and may be unreliable for monitoring of malignancies in these patients while other markers evaluated (AFP, PSA and CA 19.9) appear to maintain their specificity in these situations.

Keywords: Hemodialysis, Kidney Transplantation, Tumor Markers

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INTRODUCTION

Although kidney transplantation is an effective treatment for end-stage renal disease, dialysis is still the commonest treatment for such patients. Patients maintained on dialysis are potentially at increased risk of cancer for several reasons, including: Secondary immune deficiency, previous treatment with immunosuppressive or cytotoxic drugs, underlying kidney disease, uremic toxins, hyperparathyroidism, nutritional deficiencies, and altered DNA repair (1,2,3).

The greatest incidence of cancer has been observed in younger patients and with increasing age the incidence progressively declines. Major malignancies in patient on dialysis are cancer of kidney, bladder, thyroid, tongue, liver, cervix, and uterus as well as Hodgkin's disease and multiple myeloma (3,4,5). The incidence of neoplasia is 0.4-27 times greater than normal population in a comparable age group (6,7,8,9,10).

Increased risk of cancer after kidney transplantation is well documented and the main contributing factor is thought to be the prolonged use of immunosuppressive drugs. The incidence of neoplasia is about 80 times greater than normal population. The average interval for appearance of tumor is 29 months after transplantation. Squamous cell carcinoma or basal cell carcinoma, in-situ carcinoma of the cervix, carcinoma of the lip and a variety of other tumors like lymphoma and reticular cell carcinoma may appear in these patients. (11,12,13)

Tumor markers are considered as significant diagnostic and prognostic factors in the evaluation of various neoplasias. Under normal conditions the levels of these molecules remain low and their metabolism has not been fully clarified. There are only a few published reports on tumor markers in patients on dialysis and post-transplantation.

In this study the level of several tumor markers are evaluated and compared in patients undergoing chronic hemodialysis, successfully transplanted and normal controls.

PATIENTS AND METHODS

Patients. Eighty nine individuals, without any clinical signs and symptoms of neoplasia were studied. They were divided to three groups as follow: Group A consisted of 30 chronic uremic patients who had been on hemodialysis for at least 6 months, group B and C consisted of 29 transplanted patients and 30 normal individuals as controls, respectively.

Tumor markers assay. Using ELISA method, the following six tumor markers were measured: Alpha-Feto protein (AFP) (RADIM-SPA-Haly):

a marker for liver, ovary and testes cancers. Carcinoembryonic antigen (CEA) (EQUIPAR-Srl-Haly): a marker for breast, lung and gastrointestinal cancers, CA 19-9 (Can Ag Diagnostic AB, SWEDEN): a marker for pancreatic cancer, CA 125 (Can Ag Diagnostic AB, SWEDEN): a marker for ovarian cancer, CA 15-3 (Can Ag Diagnostic AB, SWEDEN): a marker for breast cancer, PSA (Can Ag Diagnostic AB, SWEDEN): a marker for prostatic cancer. The cut off values of these markers were as follow:

CEA <5 µg/L
CA125 <35 U/ml
CA19-9 <37 U/ml
CA15-3 < 30 U/ml
AFP < 5 ng/ml
PSA < 4 µg/L

Statistical analysis. The results were analyzed by means of t-test, Anova, Duncan, One way tests and also regression analysis. Values of $p<0.05$ were considered statistically significant.

RESULTS

The mean age of patients on hemodialysis (group A) was 16.5 ± 6.2 years of which 53% were males. Renal failure was secondary to reflux nephropathy and obstructive disorders in 30%, inherited diseases (Alport's Syndrome – cystinosis – nephronophthisis -oxalosis) in 20%, chronic glomerulonephritis in 26% and unknown etiology in 24% of cases. The duration of chronic renal failure and hemodialysis were 3.15 ± 2.2 years and 3.2 ± 2.4 years, respectively. Sessions of dialysis per week was 2.03 ± 0.85 with dialysis adequacy (kt/v) of 0.94 ± 0.32. The mean of blood pressure in these patients was 119.83 ± 22.45 / 75.66 ± 12.78 mm/Hg. In kidney transplantation

Table 1. Demographic information of the hemodialysis group.

Age	16.5 ± 6.2 (yr) (F=47% , M=53%)
Etiology of CRF	Reflux Nephropathy (30%)
	Inherited diseases (20%)
	GN (26%)
	Unknown (24%)
Duration of CRF	3.15 ± 2.2 (yr)
Duration of HD	3.2 ± 2.4 (yr)
HD/Wk	2.03 ± 0.85
Adequacy of HD (kt/v)	0.9 ± 0.32
BP	119.83 ± 22.45/75.66 ± 12.78 (mm/Hg)

(group B) the mean age was 12.51 ± 2.5 years with 62% male, the mean age of donors was 29.75 ± 7.1 years. Renal failure was secondary to reflux nephropathy and obstructive disorders in 52%, inherited diseases (cystinosis- Alport- polycycstic kidney disease) in 14% and chronic glomerulonephritis in 34%. The duration of pre-transplantation chronic renal failure and hemodialysis were 3.1 (2.6 and 1.2 ± 1 years, respectively. The mean of post-transplantation serum creatinine was 1.6 ± 1.1 mg/dl and duration of kidney transplantation was 2.25 ± 1.2 years. Their sources of donors were from cadaver, unrelated and related in 27%, 42% and 31%, respectively. Mean of their acute reversible rejections were 0.48 ± 0.4 and mean of their blood pressure was 115.69 ± 20.64 / 77.58 ± 12.72 mm/Hg.
The demographic data of study populations are summarized in tables 1 and 2. There were no significant fluctuations in the level of tumor markers CA19-9, AFP, and PSA in the study population and the control group. The level of tumor marker CA125 was significantly higher in the hemodialysis and

Table 2. Demographic information of the transplantation group.

Age (Recipient)	12.51 ± 2.5 (yr) (F=38%, M=62%)
Age (Donor)	29.75 ± 7.1 (yr)
Etiology of CRF)	Reflux Nephropathy (52%)
	Inherited diseases (14%)
	GN(34%)
Graft Function (S creat.)	1.6 ± 1.1 (mg/dl)
Duration of CRF	3.1 ± 2.6 (yr)
Duration of HD	1.2 ± 0.5 (yr)
Duration of TX	1.2 ± 0.5 (yr)
Graft	Cadaver (27%)
	Related (31%)
Rejection	0.48 ± 0.4
BP	115.69 ± 20.64 / 77.58 ± 12.72 (mm/Hg)

kidney transplanted groups when compared to normal controls.
The tumor markers CA15-3 and CEA were significantly higher in hemodialysis group but in kidney transplantation these markers did not show any significant difference with normal controls. The level of these tumor markers is summarized in Table 3.

DISCUSSION

The results of this study suggest that hemodialysis and kidney transplantation

Table 3. Levels of tumor markers in three groups

Tumor markers	Group	Number	Mean	Minimum	Maximum	Increased%	Normal%
CEA	HD	30	2.43	0.9	7.9	6.7	93.3
(<5 µg/L)	TX	29	1.69	0.9	3.8	0	100
	Control	30	1.63	0.9	3	0	100
	Total	89	1.92	0.9	7.9	2.2	97.8
PSA	HD	30	0.34	0.2	2	0	100
(<4 µg/L)	TX	29	0.25	0.2	1	0	100
	Control	30	0.57	0.2	11	3.3	96.7
	Total	89	0.39	0.2	11	1.1	98.9
AFP	HD	30	0.1	0.1	1	0	100
(<5 ng/ml)	TX	29	0.2	0.1	3	0	100
	Control	30	0.23	0.1	4	0	100
	Total	89	0.17	0.1	4	0	100
CA19-9	HD	30	12.94	0.1	57	3.3	96.7
(<37 U/ml)	TX	29	12.45	0.1	30	0	100
	Control	30	11.15	0.1	43	3.3	96.7
	Total	89	12.83	0.1	57	2.2	97.8
CA125	HD	30	25.30	0.1	252	13.3	86.7
(<35 U/ml)	TX	29	36.68	0.1	480	13.8	86.2
	Control	30	12.98	0.1	58	6.7	93.3
	Total	89	24.85	0.1	480	11.2	88.8
CA15-3	HD	30	19.76	3	38	13.3	86.7
<30 U/ml	TX	29	22.10	6	57	6.9	93.1
	Control	30	17.50	5	38	6.7	93.3
	Total	89	19.76	3	57	9	91

in patients with end-stage renal failure may alter the levels of certain tumor markers. Specifically CA125 was elevated in hemodialysis and kidney transplanted groups but CEA and CA15-3 were elevated only in hemodialysis group. A plausible explanation of this observation could be that healthy renal tissue is involved in metabolism and clearance of at least some tumor markers. These fluctuations in the level of tumor markers in hemodialysis and kidney transplantation have been reported by various investigations.Cases et al. (13), Polenakovic (14) and Filella (15) have also found higher levels of CEA in hemodialyzed patients when compared to normal individuals. Moreover, they observed that the levels of CA125, CA19-9, CA15-3, AFP and PSA tend to be in normal range in this group.

Concerning AFP our results differ from those of Zeferos et al. (11) who observed that the elevation of AFP level parallels those of CEA in hemodialysis group, but it is similar to results of Cases et al. (13), Arik et al. (16), Odagiri et al. (17), Lye et al. (18), Oberbauer et al. (19) who observed normal levels of these markers in hemodialysis and kidney transplantation groups.

CA 125 was significantly higher in hemodialysis and kidney transplantation groups in our study, these results are similar with those of Arik et al. (16), Lye et al. (18) Oberbauer et al. (19) and Wood et al. (20) while differ from those of Zeferos et al. (11), Cases et al. (13), Polenakovic et al. (14), Filella et al. (15), Odagiri et al. (17) and Menzin et al. (21) who observed normal levels of these tumor markers in these patients. CA19-9 was in normal range in our study that is similar to the results of Cases et al. (13), Filella et al. (15), Odagiri et al. (17) and Oberbauer et al. (19) studies but different with Polenakovic et al. (14), Arik et al. (16), Lye et al. (18) and Wood et al. (20) studies who observed significantly high levels of these tumor markers in their patients.

Regarding CA15-3 our result show higher level of this marker in hemodialyzed patients when compared to transplanted group and normal controls, but differ from those of Cases et al. (13), Polenakovic et al. (14), Filella et al. (15), Odagiri et al. (17), Oberbauer et al. (19) and Wood et al. (20) who observed normal level of this marker in their patients, although Zeferos et al. (11) observed higher level of this tumor marker in kidney transplantation.

Regarding PSA levels, our result is similar to those of Cases et al. (13), Polenakovic et al. (14), Arik et al. (16), Lye et al. (18), Harper et al. (22) and Morton et al. (23) who observed normal level of this marker in their patients, but differs from Oberbauer et al. (19), Sasagawa et al. (24) and Djavan et al. (25) studies who observed high level of this marker in hemodialyzed group.

In hemodialysis and kidney transplantation, several tumor markers are elevated above reference values in a substantial number of patients, making them unreliable for monitoring of malignancies in these groups, while the other markers evaluated appear to maintain their specificity.

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