Testosterone Level in Testicular Cancer Patients after Chemotherapy

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ABSTRACT

Background: The use of chemotherapy for the treatment of cancer began at the start of the 20th century in an attempt to narrow the universe of chemicals that affect the disease. Metastatic testicular cancer has always been sensitive to chemotherapy.

Subjects and Method: A retrospective and prospective study was performed of patients who had undergone testicular cancer from 2011–2013. The overall age of the testicular cancer patients at the time of diagnosis, their marital status, stage of disease and treatment strategies, testosterone level etc were analysed using linear regression and t-*test.*

Results: Most of the patients had seminoma tumour. A greater number of patients were diagnosed in the later stages of the disease. Before chemotherapy, testosterone level was normal and decreased during chemotherapy but after completion, it returned to normal level.

Conclusion: There is an early onset of testicular cancer in the Pakistani population. There is no effect of chemotherapy on testosterone production in late survivors.

Keywords: Testicular cancer, chemotherapy, testosterone, tumour

Nivel de Testosterona en Pacientes con Cáncer Testicular después de la Quimioterapia

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RESUMEN

Antecedentes: El uso de la quimioterapia para el tratamiento del cáncer comenzó a principios del siglo XX, en un intento por reducir el universo de productos químicos que afectan la enfermedad. El cáncer testicular metastásico ha sido siempre sensible a la quimioterapia.

Sujetos y método: Se realizó un estudio retrospectivo y prospectivo de pacientes que habían sufrido cáncer testicular en el período 2011–2013. La edad general de los pacientes de cáncer testicular en el momento del diagnóstico, su estado civil, etapa de la enfermedad y tratamiento, estrategias de nivel testosterona, etc. se analizaron mediante regresión lineal y prueba t.

Resultados: La mayoría de los pacientes tenían tumores seminomas. Un mayor número de pacientes fue diagnosticado en las etapas avanzadas de la enfermedad. Antes de la quimioterapia, el nivel de testosterona fue normal y disminuyó durante la quimioterapia, pero una vez terminada, volvió al nivel normal.

Conclusión: Hay un inicio temprano del cáncer testicular en la población paquistaní. No hay efecto de la quimioterapia sobre la producción de testosterona en los supervivientes tardíos.

Palabras claves: Cáncer testicular, testosterona, quimioterapia, tumor

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INTRODUCTION

Testicular cancer is an abnormal growth of cells in the testicles. It is most common in men 15 to 35 years old (1). More than 95 per cent of all men survive the disease (2, 3). For the diagnosis of disease, the International Germ Cell Cancer Collaborative Group (IGCCCG) classification is currently used in clinical practice (4). It is hypothesized that the disease process

starts in fetal life and consists of abnormal proliferation of primordial germ cells (1, 5) and peak incidence is in the younger age groups, but the majority is seen in the third decade (6). Different risk factors such as reduced feedback inhibition of the gonadal-hypothalamic-pituitary axis, testicular atrophy and injury, increased gonadotrophin decline and cryptorchidism are involved in the development of a testicular tumour (7, 8). Low parity is considered a stronger risk factor for testicular cancer (9). Surgery, radiation therapy and chemotherapy are the treatment for this disease (10). Anticancer drugs are recommended when there are signs that the cancer has spread. Bleomycin, etoposide and cisplatin are the standard treatment for testicular germ cell cancer patients (11). Blood components will decrease after chemotherapy, but at different speeds (12). Testicular cancer affects mostly young people; they can survive after treatment, but they may experience negative impacts on their quality of life, such as hormonal disturbances (12). The aim of the present study was to investigate the effects of chemotherapy on testosterone levels in testicular cancer patients. The hormone levels affected due to chemotherapy were differentiated from the effects of the tumour itself by comparing the hormone levels before the onset of chemotherapy to levels measured during and after completion of chemotherapy.

SUBJECTS AND METHODS

This was a prospective and retrospective study of men with testicular cancer, conducted during 2011–2013. The study was carried out in the Nuclear Medicine, Oncology and Radiotherapy Institute (NORI), Islamabad, and Combined Military Hospital (CMH), Rawalpindi. The study evaluated one hundred patients with histologically proven testicular cancer. Of these patients, seventy-five were diagnosed during the period of 2011–2013, while thirty previously diagnosed cases were also included in the present study.

For the estimation of testosterone, 3 mL of venous blood from each subject was collected then allowed to clot at room temperature. After clotting, blood was centrifuged at 3000 rpm (revolutions per minute) for 10 minutes. The serum was then separated in labelled tubes and frozen at -20 °C for

the estimation of testosterone. Testosterone EIA test kit (BioCheck Inc, CA, USA), catalogue number BC-1115, was used to determine testosterone concentrations.

Statistical analysis

Percentage, mean, standard error of mean, linear regression, and t-test for percentages were calculated for different parameters. Graph Pad version 5 was used for statistical analysis.

RESULTS

This study is based on data from 100 patients diagnosed with testicular tumour. The age group of testicular cancer patients at the time of diagnosis is shown in Table 1. Patients were divided into six age groups, with an interval of 10 years. Majority of the patients were between the ages of 21 and 30 years (n = 38; 38%) with a mean age of 25.68 ± 0.47 years.

The mean age of married and unmarried patients is shown in Table 1. In the age group of 21–30 years, there were significantly more unmarried patients ($p < 0.04$) as compared to married patients.

The types of testicular tumour in married and unmarried patients in different age groups are shown in Table 2. In the age group of 21–30 years, the highest number was unmarried patients (16.90%) with seminoma tumour, while the lowest number of patients (1.41%) was observed with teratoma. All the patients were married in the age groups of 31–40 and 41–50 years. The highest percentage of married patients (18.31%) was observed with seminoma tumour and the lowest number of patients (1.41%) was observed with mixed germ cell tumour at 31–40 years, while 11.26% of patients with seminoma and 1.41% patients with embryonal carcinoma were observed in the age group of 41–50 years.

The majority of patients (63.89%) having a child was diagnosed with seminoma tumour, but the lowest number (2.77%) of these patients was observed with yolk sac tumour. The majority of patients (61.11%) having no children was diagnosed with seminoma tumour, but the lowest number (11.11%) of patients was observed with teratoma and embryonal carcinoma (Fig. 1).

Table 1:   Mean age (years) and percentages of testicular tumour patients according to different age groups and marital status

Age groups	All Percentage (n)		All Mean age	Married Percentage (n)		Married Mean age	Unmarried Percentage (n)		Unmarried Mean age
1–10	5	(5)	02.80 ± 1.10	–		–	11.11	(5)	02.80 ± 1.10
11–20	14	(14)	17.64 ± 0.56	–		–	31.11	(14)	17.18 ± 0.63
21–30	38	(38)	25.68 ± 0.47	21.82	(12)	25.08 ± 0.54	57.77	(26)	27.00 ± 0.84
31–40	22	(22)	35.18 ± 0.52	40.00	(22)	35.05 ± 0.55	–	–	
41–50	12	(12)	45.91 ± 0.83	21.82	(12)	44.78 ± 1.06	–	–	
51–60+	9	(9)	59.11 ± 2.26	16.36	(9)	59.11 ± 2.26	–	–	
Total	**100**	**(100)**		**100.0**	**(55)**		**100.00**	**(45)**	

Table 2:   Percentage of married and unmarried patients according to different age groups (years) with different types of testicular tumour

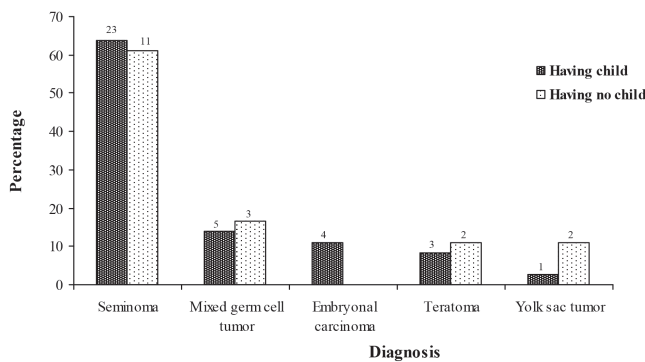| Diagnosis	Married (Age groups)			Unmarried (Age groups)		
	21–30 (n)	31–40 (n)	41–50 (n)	21–30 (n)	31–40 (n)	41–50 (n)
Seminoma	8.45% (6)	18.31% (13)	11.26% (8)	16.90% (12)	–	–
Mixed germ cell tumour	7.04% (5)	01.41% (1)	02.82% (2)	11.26% (8)	–	–
Embryonal carcinoma	–	04.22% (3)	01.41% (1)	04.22% (3)	–	–
Teratoma	–	04.22% (3)	–	01.41% (1)	–	–
Yolk sac tumour	1.41% (1)	02.82% (2)	–	02.82% (2)	–	–
Total	**12**	**22**	**11**	**26**	**–**	**–**

Fig. 1:   Number and percentage of patients with and without children according to different types of testicular tumour.

Site of origin of testicular tumour

The tumour site of 87 patients was determined by the clinical reports. Of the 87 patients, 83 (95%) had unilateral and 4 (4.59%) had bilateral tumour. In unilateral tumour, the left side of the testis was commonly affected by the cancer in 36 (41.37%), while right testicular cancers were found in 32 (36.78%) subjects. There were 15 (17.24%) patients whose record regarding the site of involved testis was not mentioned in their hospital clinical record; they were mentioned as unilateral (Table 3).

The highest number of patients was diagnosed with seminoma cancer stage II (26.04%) followed by stage I (17.70%) and the lowest number of patients was at stage III (8.33%). In embryonal carcinoma, 3.12% of patients were at stage I, while at stage II and stage III, 7.29% and 1.04% of patients were observed, respectively. For teratoma tumour patients at stage I, stage II and stage III, the percentage of patients observed was 5.21%, 1.04% and 4.16%, respectively. In mixed germ cell tumour, the number of patients at stage I was 7.29%, at stage II, 8.33% and at stage III, 2.08%. At stage I

Table 3:   Number and percentage distribution of patients suffering from different types of testicular tumour on the basis of site of origin

Diagnosis	Left side	Right side	Unilateral (Unknown)	Bilateral	Total
	Percentage (n)	Percentage (n)	Percentage (n)	Percentage (n)	n
Seminoma	26.44 (23)	21.84 (19)	04.59 (4)	02.29 (2)	48
Mixed germ cell tumour	09.19 (8)	02.29 (2)	03.44 (3)	01.14 (1)	14
Embryonal carcinoma	02.29 (2)	04.59 (4)	02.29 (2)	01.14 (1)	9
Teratoma	01.14 (1)	05.74 (5)	03.44 (3)	–	9
Yolk sac tumour	02.29 (2)	02.29 (2)	03.44 (3)	–	7
Total	**41.37 (36)**	**36.78 (32)**	**17.24 (15)**	**04.59 (4)**	**87**

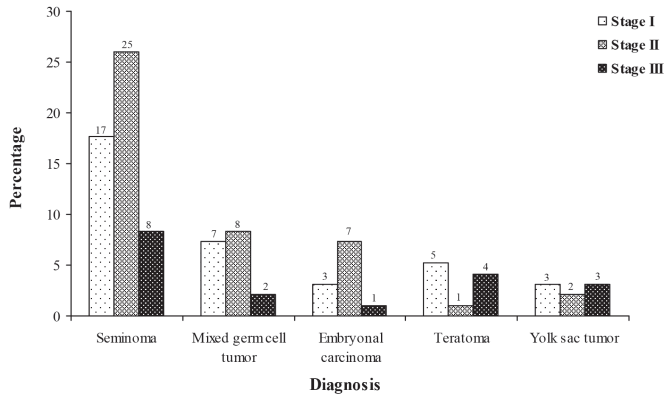and stage III in yolk sac tumour, 3.12%, but at stage II, 2.08% of patients were observed (Fig. 2).

Fig. 2: Number and percentage of patients diagnosed with different types of testicular tumour according to stages of the disease.

Treatment for different types of testicular cancer

Patients diagnosed with different testicular tumour types were given courses of treatment such as chemotherapy, radiotherapy, both (chemotherapy and radiotherapy) and none (Table 4). Most patients were given both chemotherapy and radiotherapy treatment cycles. The majority of patients (52%) with seminoma tumour received the drug regimen bleomycin, etoposide, cisplatin (BEP), but only 36.36% of patients with embryonal carcinoma received this drug regimen. Only patients with mixed germ cell tumours (5.55%) and teratomas (10%) received the etoposide and cisplatin (EP) drug regimen. Fourteen per cent of patients did not receive any drug treatment.

Treatments for testicular tumour types diagnosed at different stages are shown in Table 5. The highest number of average chemotherapy cycles (3.5 ± 0.63) was given at stage II for those with seminoma, while the lowest number of average chemotherapy cycles (1.5 ± 0.29) was given at stage II of

Table 4: Treatment regimens for patients with different types of testicular cancer

Diagnosis (n)	Mean cycles (n)				Drugs (n)			
	Chemotherapy	Radiotherapy	Both	None	BP	BEP	EP	NO
Seminoma (50)	2.77 ± 0.44 (18)	1.75 ± 0.48 (4)	6.58 ± 0.73 (24)	(4)	32.00% (16)	52.00% (26)	–	16.00% (8)
Mixed germ cell tumour (18)	1.67 ± 0.24 (5)	–	6.18 ± 1.23 (11)	(2)	27.77% (5)	55.55% (10)	05.55% (1)	11.11% (2)
Embryonal carcinoma (11)	3.00 ± 1.00 (3)	–	8.00 ± 1.62 (7)	(1)	54.54% (6)	36.36% (4)	–	09.09% (1)
Teratoma (10)	2.25 ± 1.25 (4)	–	6.40 ± 1.44 (5)	(1)	20.00% (2)	60.00% (6)	10.00% (1)	10.00% (1)
Yolk sac tumour (9)	1 (1)	1 (1)	8.50 ± 4.20 (6)	(1)	–	77.77% (7)	–	22.22% (2)

BP: bleomycin and etoposide; BEP: bleomycin, etoposide and cisplatin; EP: etoposide and cisplatin; NO: no drugs

Table 5: Treatment regimens for patients with different types of testicular cancer according to stage of disease

Diagnosis (n)	Stage (n)	Mean cycles (n)				Drugs (n)			
		Chemo	Radio	Both	None	BP	BEP	EP	NO
Seminoma (50)	I (17)	2.33 ± 0.62 (9)	3 (1)	3.83 ± 0.70 (6)	(1)	23.52% (4)	64.70% (11)	–	11.76% (2)
	II (25)	3.50 ± 0.63 (8)	1 (1)	8.28 ± 0.91 (14)	(2)	40.00% (10)	48.00% (12)	–	12.00% (3)
	III (8)	1 (1)	1.5 ± 0.5 (2)	4.75 ± 1.66 (4)	(1)	25.00% (2)	37.50% (3)	–	37.50% (3)
Mixed germ cell tumour (17)	I (7)	2 (1)	–	6.50 ± 1.58 (6)	–	57.14% (4)	42.85% (3)	–	–
	II (8)	1.50 ± 0.29 (4)	–	4.50 ± 2.18 (4)	–	12.50% (1)	75.00% (6)	–	50.00% (1)
	III (2)	–	–	11 (1)	(1)	–	50.00% (1)	–	50.00% (1)
Embryonal carcinoma (11)	I (3)	2.50 ± 1.5 (2)	–	4 (1)	–	66.67% (2)	33.33% (1)	–	–
	II (7)	4 (1)	–	10.0 ± 1.38 (5)	(1)	57.14% (4)	28.57% (2)	–	14.28% (1)
	III (1)	–	–	3 (1)	–	–	100.0% (1)	–	–
Teratoma (10)	I (5)	1 (3)	–	2 (1)	(1)	40.00% (2)	40.00% (2)	–	20.00% (1)
	II (1)	6 (1)	–	–	–	–	100.0% (1)	–	–
	III (4)	–	–	7.5 ± 1.19 (4)	–	–	75.00% (3)	25% (1)	–
Yolk sac tumour (9)	I (3)	–	–	2 (2)	(1)	–	66.66% (2)	–	33.33% (1)
	II (2)	–	1 (1)	4 (1)	–	–	50.00% (1)	–	50.00% (1)
	III (3)	1 (1)	–	7 (2)	–	–	100.0% (3)	–	–
	NO (1)	–	–	29 (1)	–	–	100.0% (1)	–	–

BP: bleomycin and etoposide; BEP: bleomycin, etoposide and cisplatin; EP: etoposide and cisplatin; NO: no drugs

mixed germ cell tumours. Stage II embryonal carcinoma had the highest number of average combined chemotherapy and radiotherapy cycles (10 ± 1.38); this was lowest (3.83 ± 0.70) for stage I seminoma. The majority of patients with stage II testicular tumour received the drug regimen BEP, while the lowest number of patients at stage III also received this drug regimen.

Testosterone levels and blood cell count during chemotherapy cycles

Testosterone levels before, during and after chemotherapy for patients diagnosed with different testicular tumours are shown in Table 6. Regression analysis of variance showed a significant (b = -0.5660 ± 0.05725, $F_{(1, 2)}$ = 97.75, p = 0.0022) decrease in mean testosterone level during chemotherapy cycles, which returned to normal level after the completion of chemotherapy [six cycles] (Fig. 3).

Table 6:   Testosterone levels (mean ± SE) in testicular tumour patients during different chemotherapy cycles

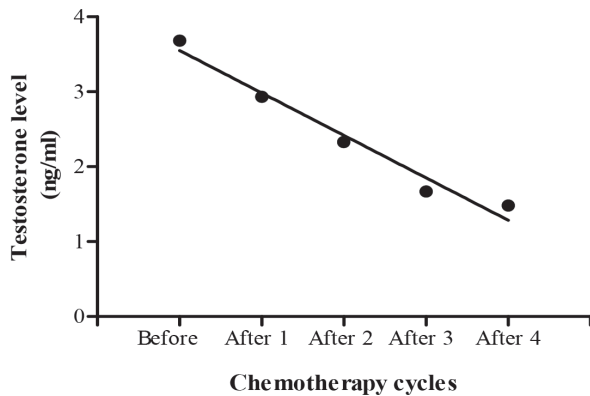| Chemotherapy cycles	Testosterone level	(n)
Before chemotherapy	3.68 ± 1.02	(15)
After 1st cycle	2.93 ± 0.36	(12)
After 2nd cycle	2.33 ± 0.63	(10)
After 3rd cycle	1.67 ± 0.58	(10)
After 4th cycle	1.48 ± 0.36	(10)
After 6th cycle	3.80 ± 0.29	(18)

Fig. 3:   Calculated regression line indicating decrease in testosterone level during different chemotherapy cycles.

The blood cell count in testicular tumour patients before, during and after chemotherapy cycles are shown in Table 7. A significant (b = -296.2 ± 113.3, $F_{(1, 2)}$ = 6.840, p = 0.0474) decrease in mean white blood cells during different chemotherapy cycles was shown by regression analysis of variance (Fig. 4), but there was no significant (b = -0.08000 ± 0.06239,
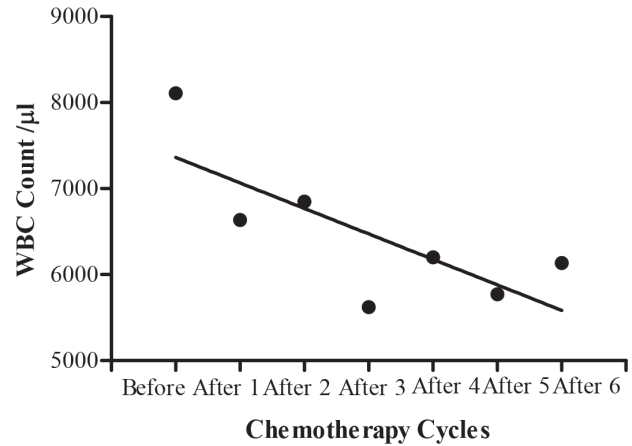

Fig. 4:   Calculated regression line indicating decrease in while blood cell (WBC) count during different chemotherapy cycles.

$F_{(1, 2)}$ = 1.644, p = 0.2560) decrease in haemoglobin level (Fig. 5). Regression analysis of variance showed a significant (b = -146300 ± 56180, $F_{(1, 2)}$ = 6.785, p = 0.0480) decrease in
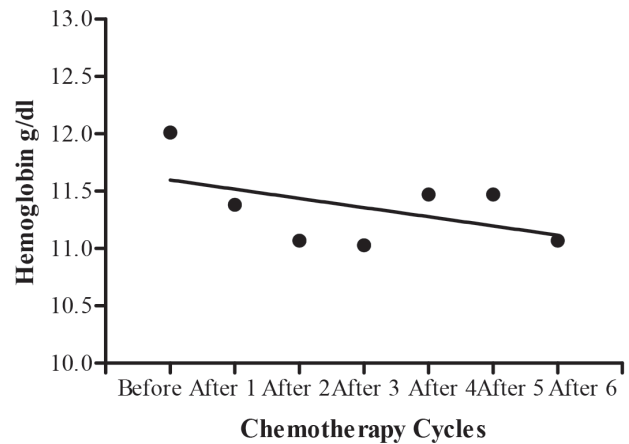

Fig. 5:   Calculated regression line indicating no decrease in haemoglobin level during different chemotherapy cycles.

Table 7:   Blood cell count (mean ± SE) in testicular tumour patients during different chemotherapy cycles

Chemotherapy cycles	(n)	WBC	RBC	HB	Platelets
Before chemotherapy	(76)	8109.20 ± 340.06	4541974 ± 084663.8	12.01 ± 0.24	386378.4 ± 88398.32
After 1st cycle	(50)	6633.40 ± 560.16	4308000 ± 136046.8	11.38 ± 0.28	349700.0 ± 23462.30
After 2nd cycle	(43)	6848.84 ± 565.16	4900233 ± 084211.8	11.07 ± 0.27	392907.0 ± 32867.68
After 3rd cycle	(35)	5620.00 ± 346.48	3914571 ± 084353.5	11.03 ± 0.26	298857.1 ± 27152.33
After 4th cycle	(28)	6200.00 ± 615.17	3951429 ± 077779.5	11.47 ± 0.22	320500.0 ± 33616.75
After 5th cycle	(24)	5770.83 ± 590.76	3869167 ± 136983.4	11.47 ± 0.44	280416.7 ± 19502.50
After 6th cycle	(14)	6135.71 ± 683.52	3785000 ± 1633793.5	11.07 ± 0.39	226642.9 ± 15497.11

WBC: white blood cell; RBC: red blood cell; HB: haemoglobin

mean red blood cells during different chemotherapy cycles (Fig. 6). There was also a significant (b = -24650±5534, $F_{(1, 2)}$ = 19.84, p = 0.0067) reduction in platelet cells during chemotherapy (Fig. 7).
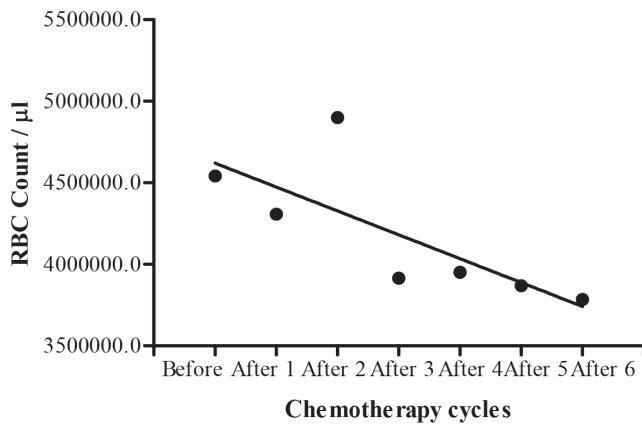

Fig. 6: Calculated regression line indicating decrease in red blood cell (RBC) count during different chemotherapy cycles.
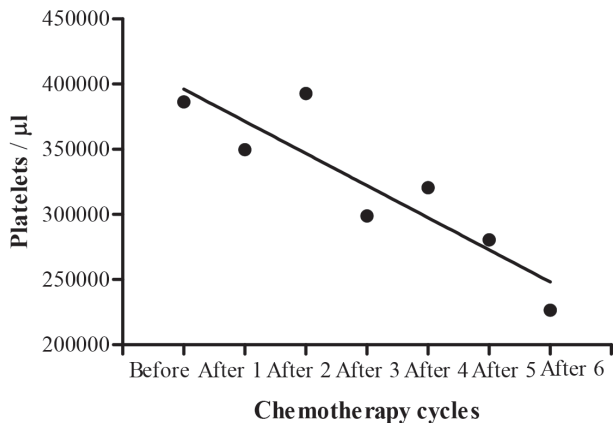

Fig. 7: Calculated regression line indicating decrease in platelet cells during different chemotherapy cycles.

DISCUSSION

The present study of 100 men with testicular cancer was conducted during 2011–2013. The age at diagnosis in the present study ranged from 1 to 70 years and mean age was 31.05 ± 1.39 years. This finding is in confirmation with the study by Bhurgri *et al* from Hyderabad (Pakistan) who stated that the mean age for testicular cancer is 31.9 years, while the age range was 3 to 65 years (13). In another study, Raman *et al* reported that the mean age was 32.6 years and age range was 25 to 52 years (14). The peak incidence was observed at 21–30 years in the present study, similar to the study by Naqvi *et al* from Nawabshah (Pakistan) who stated that testicular tumour patients were affected mostly in this age group (6).

For the histological classification of testicular cancer, clinical data presented an incidence of 50% for seminoma,

which is similar to another report (15). No significant difference was observed between married and unmarried patients for risk of testicular cancer in the present study. In a study in London, it was also observed that there was no association between risk of cancers and marital status for ever *versus* never married (16). Most of the patients (67%) with testicular cancers have children but not more than two or three. Similar findings were observed in two different stud-ies, Moller and Skakkbaek in Denmark and Baker *et al*, who reported in their study that those who have only one child or no children were at a greater risk of testicular cancers (17, 18). In another study conducted in Sweden, it was observed that increasing sibship size was associated with a reduced risk of testicular germ cell cancer (19). Almost one-third (31.71%) of patients were diagnosed at stage I, which is contradictory to the study of Powles *et al* who described that the patients with stage I disease were more compared to other diagnosed stages and this was due to improved education and awareness of germ cell tumours, resulting in earlier diagnosis. The incidence of testicular cancer at stage I in seminoma was 17% and in non-seminoma it was 11% in the present study, similar to the study of Powles *et al* in the UK who observed that nonseminomas developed from seminomas (20). The mean age at stage I was highest as compared to other stages (II and III) in the present study. Regarding the site of origin of testicular tumour, bilateral tumours were observed in 4.59% patients at the time of diagnosis. Similar findings were observed in two different studies in which bilateral testicular germ cell tumours ranged between 1 and 5%. Risk for bilateral germ cell tumours was low because when the unilateral tumour was diagnosed, it was treated by chemotherapy and radiotherapy; this resulted in a cure in most cases, with very low chances of developing a tumour in the contralateral testis (21, 22).

In the present study, the sera from 75 subjects were assayed before treatment, during different chemotherapy cycles and after the completion of chemotherapy cycles. It was observed that testosterone level was normal before receiving any treatment and it decreased during chemotherapy, but returned to normal level after chemotherapy treatment completion. Similarly, Gerl *et al* observed that testosterone levels decreased significantly in patients who received chemotherapy (23). While some studies reported that testosterone level was not any different between healthy men and those with testicular cancer (24), Meinardi *et al* reported that chemotherapy-treated cancer patients had a significant increase in cardiac risk factors such as hyperlipidaemia, renal insufficiency, increased body mass index, hypertension and metabolic syndrome, and these may relate to hormonal changes, such as testosterone deficiency, caused by the combination of orchidectomy and chemotherapy treatment (25). Pectasides *et al*, as reported in a study in Greece, found that testosterone levels remained within the normal range after chemotherapy (26). The testosterone levels within normal range in patient groups indicate that high dose chemotherapy does not induce complete Leydig cell failure (27).

Bleomycin, etoposide and cisplatin (BEP) chemotherapy was most commonly used for testicular patients in the current study and etoposide, cisplatin (EP) combination was used for few patients. A study conducted in Japan also found that BEP is the standard treatment option for testicular cancer due to low toxicities and high cure rate, while EP is used only for those patients whose disease was complicated by active asthma (28). Culine *et al* demonstrated that BEP and EP were both regimens used as standard of care in patients with a lower stage of disease (29).

In conclusion, most of the patients were diagnosed histologically as seminoma tumour. A larger number of patients was diagnosed at later stages of disease. Therefore, great effort is required to educate the population about self-examination and knowledge of the disease. Most of the patients received both chemotherapy and radiotherapy cycles and the most common drug regimen was BEP. This study demonstrates that testosterone level decreases during chemotherapy cycles, but returns to normal level after the completion of chemotherapy.

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APPENDIX
Data sheet

Laboratory evaluations and clinicopathological features of patients were recorded on the following data sheet.

Date ———— Reference No. ————
Hospital ————

Patient profile
Subject name ————   Occupation ————
Age at diagnosis ————   Present age ————

Presentation
Testicular swelling ———   Pain in abdomen ———
Abdominal mass————   Weight loss ————

Family history
Close relative with cancer ————
Type of cancer————————

Obstetric history
Marital status ————————
Smoking————————
No. of children ————————

Past medical history
Undescended testis ————————   Mumps in childhood ————
Orchidectomy ————————   Hepatitis ————————
Tuberculosis ————————

Present medical history
Presenting complaints ————
Diagnostic procedure ————

Present disease
Stages ————   Unilateral ————
Bilateral ————   Malignant ————

Treatment
Chemotherapy ————   Drugs ————
Radiotherapy ————   Cycle ————
Surgery ————   Follow up ————

Histopathology hormone
Testosterone ————

Blood picture
WBC ————————   RBC ————
HB ————————   Platelets ————