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Original Article

To Study Level of Gonadal Hormone in Cancer Patients Receiving Chemotherapy

Ashok Asaram Meshram[1], Subhash Ranjan[2], Rajendra Singhal[3], Walmik Shrihari Yegade[4], Gopi Dummu Krishna[5]

[1]Department of Medicine and Hematology, Command Hospital (Eastern Command), Kolkata, West Bengal, [2]Department of Medicine and Oncology, Sushruta Hospital, Mumbai, Maharashtra, [3]Department of Medicine, Icon Hospital, Burhanpur, Madhya Pradesh, Departments of [4]Medicine and [5]Internal Medicine, Command Hospital (Eastern Command), Kolkata, West Bengal, India.

***Corresponding author:**
Walmik Shrihari Yegade,
Department of Medicine,
Command Hospital
(Eastern Command), Kolkata,
West Bengal, India.

yegadewalmik@gmail.com

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ABSTRACT

Objectives: The objective of this study was to study the alteration in levels of testosterone, luteinising hormone (LH), follicle-stimulating hormone (FSH) and prolactin in male cancer patients' post-chemotherapy who have been started on drugs causing grade III or more haematological toxicity requiring granulocyte colony-stimulating factor support.

Materials and Methods: An open-labelled prospective single-centre study for the assessment of Gonadal dysfunction in male cancer patients on chemotherapy from August 2010 to October 2012.

Results: Patients had a significant alteration in testosterone (23% $n = 11$), LH (52.08% $n = 25$), FSH (83.3% $n = 40$) and prolactin levels (22.92% $n = 11$) post-chemotherapy, which was statistically significant ($P < 0.05$). The high dose, as well as the low dose Cisplatin group, were associated with substantial gonadal dysfunction in testicular tumour patients. Hence, regimens using low-dose cisplatin at the cost of compromising the cure rate for the motive of preservation of fertility are not warranted. There was no statistically significant difference found in alteration in mean testosterone, mean LH or mean FSH Prolactin levels among cisplatin, cyclophosphamide or combined cisplatin and cyclophosphamide chemotherapy group, at least in the initial weeks of post-chemotherapy.

Conclusion: There is a significant gonadal dysfunction in cancer patients receiving cytotoxic chemotherapy. Hence, increasing awareness to prevent, detect and treat expected long-term toxicities is crucial. Pre-chemotherapy cryopreservation of semen and assisted reproductive technologies are good options to describe the rate of involuntary infertility without affecting the survival of patients by decreasing doses of chemotherapy.

Keywords: Gonadal dysfunction, Testosterone, Cisplatin, Fertility, Chemotherapy and survival

INTRODUCTION

In recent times, significant advances have been made in the management of various malignancies. Substantial improvements in treatment for several malignancies have directed the way toward overall survival and quality of life (QoL) of patients.[1] No doubt, with the increase in understanding of the cellular and molecular mechanisms of various cancers, the use of chemotherapeutic drugs has also increased substantially. Apart from improved clinical outcomes, adverse effects related to these drugs are also a major concern for oncologists and patients as well.[2] Cisplatin and cyclophosphamide are two common anti-cancer drugs that have shown great potency in solid and haematological malignancies.[3] However, the use of these drugs is

related to multiple adverse events such as renal dysfunction, pulmonary toxicity, cardiovascular complications and gonadal toxicities due to non-specificity toward cancerous cells. More specifically, these drugs, when administered, enter the bloodstream, travel throughout the body and kill cancer cells at their sites.[3] The drugs may rarely be intended to have a local effect, but in most cases, the intention is to destroy cancer cells wherever they may exist in the body. However, being non-specific, these drugs also cause significant damage to healthy cells and vital organs. Due to[4] the generalised action of these drugs, they also produce haematological toxicity in view of the high proliferation rate of these cells, which has been well-studied throughout the world.[5] For the management of haematological toxicities, granulocyte colony-stimulating factor (GCSF) is used.[4] Apart from haematological toxicities, gonadal toxicities are of major concern for young patients. Since the gonads contain rapidly dividing germ cells, differentiating spermatogonia proliferate rapidly, they become easy prey and extremely susceptible to cytotoxic chemotherapeutic agents, although the less active stem cell pool may also become extinct.[4] In a nutshell, these adverse vents eventually manifest into compromised clinical outcomes and reduced QoL.

Importantly, studies on this aspect of side-effects of chemotherapy are very few in India. The need for sensitisation among oncologists and cancer patients is the need of the hour so that appropriate measures can be taken to prevent fertility or paternity-related problems before chemotherapy. Considering these facts, in this study, we study the effects of chemotherapeutic drugs (Cisplatin and cyclophosphamide) alone or in combination against haematological toxicity, gonadal dysfunction and change in gonadal hormones such as follicle-stimulating hormone (FSH), luteinising hormone (LH) prolactin and testosterone. These hormones reflect the secondary effects of offending drugs on gonads if central causes have been ruled out. Moreover, we are also assessing the thyroid profile as that is one of the common causes of infertility and is easily correctable as thyroid status can be affected by chemotherapy *per se*.

Aims and objectives

Primary objectives

To study the alteration in levels of testosterone, LH, FSH and prolactin in male cancer patients post-chemotherapy who have been started on chemotherapy-containing drugs causing grade 3 or more haematological toxicity requiring GCSF support (Drugs causing grade 3 or more haematological toxicity are listed in column).

Secondary objectives

To study the difference in alteration in these hormonal profiles between the cisplatin-based chemotherapy group versus the cyclophosphamide-based chemotherapy group versus the combined cisplatin and cyclophosphamide chemotherapy group.

MATERIALS AND METHODS

Study design

This is an open-labelled prospective single-centre study of assessment of gonadal dysfunction in male cancer patients on chemotherapy. Gonadal dysfunction was assessed by observing the derangement in the level of testosterone, LH, FSH and prolactin in patients who had received chemotherapy for various cancers with GCSF support to prevent haematological toxicity. (Chemotherapy regimens used) included at least one drug causing grade 3 or more haematological toxicity. We also analysed the following subgroups for derangement in levels of testosterone, LH, FSH and prolactin in patients who were administered chemotherapy with GCSF support: (A) Testicular tumour patient, (B) non-testicular tumour patient, (C) group received cisplatin-based chemotherapy, (D) group which received low dose cisplatin (<850 mg cumulative dose of cisplatin), (E) group which received high-dose cisplatin (>850 mg cumulative dose of cisplatin, (F) group which received cyclophosphamide-based chemotherapy and (G) group which received combined cisplatin and cyclophosphamide. The study was conducted from August 2010 to October 2012.

Study population

Fifty consecutive male cancer patients aged between 14 years and 55 years with a confirmed histopathological diagnosis were considered for enrolment in the study and were followed up to 12 weeks post-chemotherapy.

Study site

The study was conducted at a tertiary care centre with permission from the Institutional Ethics Committee and informed consent from patients.

Inclusion criteria

Patients aged>14 years but <55 years and those who gave informed consent. Patients with baseline serum levels of testosterone, LH, FSH and prolactin levels hormones within the normal range were included in the study. In the case of testicular tumour patients, the baseline level of these hormone levels is normal post-orchidectomy and before the start of chemotherapy. In addition, patients who are receiving or might receive GCSF support during chemotherapy for haematological toxicity were also included in the study.

Exclusion criteria

Patients who were on chemotherapy before enrolment in the study were excluded from the study. Patients who have received radiation therapy earlier or are going to receive radiation therapy below the diaphragm during the study period, along with those who have an obvious congenital abnormality of genitals and patients with deranged thyroid function tests before the start of chemotherapy, were also excluded from the study.

Methodology

After selecting patients satisfying the necessary inclusion and exclusion criteria, all the eligible patients were interviewed, and a complete medical history was obtained. Following this, a thorough general and systematic examination was performed, and body surface area was calculated using the Mosteller formula. Baseline during and post-chemotherapy complete blood count and biochemical investigations such as liver function test, renal function test, lactate dehydrogenase, uric acid and erythrocyte sedimentation rate were carried out for staging and management purposes. For biochemical analysis, blood samples were sent for triiodothyronine, thyroxine, thyroid-stimulating hormone and testosterone, LH, FSH and prolactin levels at the radio immune assay laboratory at the same centre. Hormones like testosterone were measured by radio immune assay kit method, and LH, FSH and prolactin by immunoradiometric assay kit. Samples were maintained at 2–8°C, and if not run within 24 h of collection of samples, they were maintained at −20°C. Next, 2nd sample of blood for testosterone, LH, FSH and prolactin levels was taken 12 weeks post-chemotherapy. For the statical calculation, normal values for the hormones provided by the kit are as follows: (A) Testosterone (270–1070 ng/dL), (B) LH (1.08–8.34 mlU/mL), (C) FSH (1.50–5.84 mlU/mL) and (D) prolactin (2.9–17.1 ng/mL). The values outside this range were considered abnormal. In men, elevated basal serum FSH levels indicated germinal epithelium damage, while elevated LH levels (with/without reduced total testosterone levels) indicated Leydig cell (LC) damage.

Statistical analysis

Data were compiled and statistical analysis was carried out using Statistical Package for the Social Sciences version 16.0. Descriptive statistics was presented in percentages, means and standard deviations. Inferential statistics was presented using paired *t*-test, Wilcoxon paired test, one-way analysis of variance (ANOVA) and Mann–Whitney U rank test and $P < 0.05$ was statistically significant.

RESULTS

Observations

Of the 50 patients enrolled, two patients with deranged thyroid hormones were excluded. Out of the remaining 48 patients, 24 had had testicular tumours and 24 had non-testicular tumours. Testicular tumour patients were non-seminomatous germ cell tumours (GCTs) ($n = 15$), mixed ($n = 4$) and seminomatous GCTs ($n = 5$). None were given radiotherapy. In the non-testicular tumour group, we had non-Hodgkin's lymphoma ($n = 13$), lung cancer ($n = 2$), Ewing's sarcoma ($n = 1$), osteosarcoma ($n = 2$), head-and-neck cancers ($n = 4$), carcinoma Stomach ($n = 1$) and mesothelioma ($n = 1$). All these patients received chemotherapy requiring GCSF support.

Association between tumour types and age

The number of patients in the testicular tumour and non-testicular groups are equal, that is 24 in each group. The mean age of patients in the testicular tumour group was 31.21 + 11.53 years, and in the non-testicular tumour group, it was 36.33 + 13.05 years. The age difference between groups is not statistically significant, with $P = 0.156$. Hence, both groups were comparable, with age being not a confounding factor. The mean body weight in the testicular tumour group was 64.29 + 10.35 kg, and in the non-testicular tumour group, it was 58.02 + 10.67 kg. This difference was statistically significant, with $P = 0.04$. The mean BMI in the testicular tumour group, that is 23.15 + 2.81 kg/m^2, was higher compared to the non-testicular tumour group, which is statistically significant with $P = 0.01$.

On applying the Mann–Whitney test, the mean rank of the testicular tumour group is higher, that is 30.75, than that of the non-testicular tumour group, which suggests that the testicular tumour group had the highest Karnofsky performance scale (KPS). It can be concluded that there is a statistically significant difference between the KPS score between the testicular tumours group and the non-testicular tumours group before the start of chemotherapy (u = 138 and $P = 0.001$). None of the patients in the testicular tumour group had any addiction, and 29.2% had some form of addiction in the non-testicular tumour group.

Effect of chemotherapeutic drugs on hormone level 12 weeks post-chemotherapy

The number of patients who had deranged FSH 12 weeks post-chemotherapy was 83.33%, whereas patients who had deranged testosterone, prolactin and LH were 22.91%, 22.92% and 52.06%, respectively. The derangement in hormones was statistically significant 12 weeks post-chemotherapy with $P < 0.05$ for all four hormones.

About 64% (n = 31) of patients in the study group were in the cisplatin-only-based chemotherapy group and 19% (n = 9) in the combined cisplatin and cyclophosphamide-based group. Both were, further, divided into low- and high-dose cisplatin groups. They had approximately 42% of total number of patients (n = 48). The percentage of patients who received only cyclophosphamide-based chemotherapy was 17%. The mean testosterone levels 12 weeks post-chemotherapy were within the normal range (270–1070 ng/dL) across all the groups, irrespective of the tumour type or chemotherapy groups.

The mean FSH levels in patients receiving chemotherapy 12 weeks post-chemotherapy were raised above the upper limits of normal (1.50–5.84 mIU/mL) across all the groups, irrespective of the tumour type or chemotherapy groups. The mean LH levels 12 weeks post-chemotherapy were raised above the upper limits of normal (1.08–8.34 mIU/mL) across all the groups, irrespective of the tumour type or chemotherapy groups. The mean prolactin level 12 weeks post-chemotherapy was raised, though the mean values across all groups were within the normal range (2.9–17.1 ng/mL) irrespective of the tumour type or chemotherapy groups. The fall in testosterone levels post-chemotherapy in patients of the testicular tumour group was statistically significant, with $P < 0.05$. The rise in FSH level and prolactin was also significant, each with $P = 0.05$. The fall in testosterone levels post-chemotherapy in patients of the non-testicular tumour group was statistically significant, with $P < 0.05$. The rise in FSH, LH and prolactin was also substantial, each with $P < 0.05$.

The fall in testosterone levels post-chemotherapy in patients of only the cisplatin-based chemotherapy group was statistically significant with $P < 0.05$. The rise in FSH, LH and prolactin was also significant, each with $P < 0.05$. The fall in testosterone levels post-chemotherapy in patients of only the cyclophosphamide-based chemotherapy group was statistically significant with $P < 0.05$. The rise in FSH, LH and prolactin was also significant, each with $P < 0.05$. The fall in testosterone levels post-chemotherapy in patients of the cisplatin plus cyclophosphamide-combined group was statistically significant with $P < 0.05$. The rise in FSH level, LH level and prolactin was also significant, each with $P < 0.05$.

The fall in testosterone levels post-chemotherapy in patients of the cisplatin <850 mg chemotherapy group was statistically significant with $P < 0.05$. The rise in FSH level, LH level and prolactin was also significant, each with $P < 0.05$. The fall in testosterone levels post-chemotherapy in patients of the cisplatin >850 mg chemotherapy group was statistically significant with $P < 0.05$. The rise in FSH level, LH level and prolactin was also significant, each with $P < 0.05$. There was no statistically significant difference in alteration of mean testosterone post-chemotherapy between the cisplatin versus cyclophosphamide versus cyclophosphamide and cisplatin-combined group as determined by one-way ANOVA ($F [2,45] = 2.879$, $P = 0.067$). There was a statistically significant difference in alteration in mean LH post-chemotherapy between cisplatin versus cyclophosphamide versus cisplatin and cyclophosphamide combined groups as determined by one-way ANOVA ($F [2,45] = 2.245$, $P = 0.0.784$). There was no significant difference in mean FSH post-chemotherapy among cisplatin versus cyclophosphamide versus cisplatin and cyclophosphamide combined groups as determined by one-way ANOVA ($F [2,45] = 0.344$, $P = 0.0.710$). There was no significant difference in mean FSH post-chemotherapy among cisplatin versus cyclophosphamide versus cisplatin and cyclophosphamide combined groups as determined by one-way ANOVA ($F [2,45] = 0.416$, $P = 0.0.662$).

DISCUSSION

According to data from 93 population-based Cancer Registry in 23 European countries by EUROCARE (the widest epidemiological study on the survival of cancer patients in Europe), cancers like testicular tumours have a 10-year relative survival of about 94.3%. Others, like Hodgkin's lymphoma, have 10-year survival rates of 81.4%. It has been postulated that 1 in 250 young adults aged 20–29 will be a cancer survivor.

As many patients suffering from these cancers are young (20–40 years of age), more and more attention has been paid to possible side effects of the disease and its treatment. The reproductive function of cancer survivors, including preservation of fertility and normal sexual function, is an important issue. Furthermore, production of sex hormones may influence mental health as well as metabolic and cardiovascular function.[6] To improve the counselling of patients regarding their future life quality, research on cancer treatment side effects in relation to the function of patient's reproductive organs is needed.[6]

In this study, we have studied 50 patients between 15 and 55 years of age group and determined the alteration in gonadal and gonadotropic hormonal levels namely, testosterone, LH, follicle-stimulating hormone and prolactin 12 weeks post-chemotherapy as compared to pre-chemotherapy levels [Table 1]. These hormones reflect the fertility status of the patient, as already described in the dependence of spermatogenesis on testosterone, FSH and LH in a negative feedback manner. Patients with normal levels of these hormones before initiation of chemotherapy were only selected. This step was necessary because earlier studies already had shown the effect of cancer itself on spermatogenesis and hormonal profile. For example, testicular tumour patients diagnosed have an increased risk of being sub-or infertile.[7,8] The spermatogenesis might be defective

already before orchidectomy and deteriorates further after the same.[9] Orchidectomy is reported to cause azoospermia in up to 10% of patients.[9] Furthermore, infertile men have a high risk of developing testicular germ cell cancers. In men presenting with abnormal semen quality, a 20-fold increased risk of developing TGCC was reported.[10] Overview of data on hormonal functions in long-term survivors of testicular tumours given in a review of literature in a study by Stuart, 45% had derangement of LH and 45% had derangement of FSH post-orchidectomy, though none had low testosterone.[11] SSimilarly, studies by Brennermann *et al.* (1997), Huddart *et al*., and Jacobsen *et al.* (2001)[12-14] showed derangement of LH post-orchidectomy 6% to 12% and derangement of FSH post-orchidectomy 17–53%. Furthermore, observed that there was a derangement of testosterone post-orchidectomy in 5% and 16%, respectively.[15] These stated above had been post-orchidectomy but before chemotherapy. Hence, to remove this confounding factor, we excluded all those patients who had deranged hormonal profiles post-orchidectomy and before initiation of chemotherapy. We also excluded patients who were found to have deranged thyroid hormonal profiles since hyperthyroidism or hypothyroidism are common causes of infertility.

Testosterone

In this prospective observational study, we had 23% of total patients having low testosterone levels at 12 weeks post-chemotherapy. This observation was in concordance with the study done by where 25% post-chemotherapy in testicular cancer patients had low testosterone had also shown that (1) significant impairment of spermatogenesis exists before therapy, precluding the possibility of sperm banking in most patients, (2) combination chemotherapy in testicular tumour has substantial effects on gonadal function, rendering almost all patients azoospermic and (3) a high degree of recovery of spermatogenesis occurs sometime after 2–3 years from the initiation of treatment. Hence, many of the studies have shown no impact on testosterone of radiotherapy or cytotoxic chemotherapy in testicular tumour patients because, in almost all patients, substantial recovery occurs with standard chemotherapy regimens when followed over a long period.[16] Aass *et al.* study had follow-up period was 3 years.[15] Radiotherapy and chemotherapy had no impact on serum testosterone, and in patients with pre-treatment normal gonadal function, the risk of permanent treatment-induced toxicity is minimal after the present standard treatment.

In the present study, across all the groups, the fall in mean testosterone level post-chemotherapy was statistically significant, but the mean post-chemotherapy testosterone levels were within the normal range. This probably reflects the resistance to the cytotoxic effect of chemotherapies on LCs. Hence, multiple studies earlier reflected an increase in FSH as compared to LH levels. It was also observed that there was no statistically significant difference in fall in testosterone with the cyclophosphamide group or combined cisplatin and cyclophosphamide group. This explains that, at least in the initial period, the effect of cisplatin, cyclophosphamide and combined cisplatin and cyclophosphamide had similar effects on spermatogenesis. At this stage, further follow-up is required to assess the recovery in various chemotherapy regimens as alkylating agents like cyclophosphamide used here have been shown to render permanent infertility in patients, and agents like cisplatin, as detailed earlier, have been shown to have a good recovery.

FSH

In this study, 40 out of 48 patients had FSH 12 weeks post-chemotherapy level above the upper range of normal, which is 5.84 ml/ml, which accounts for 83.33%. This is the most common hormonal abnormality noted across all studies done earlier, even before low testosterone or raised LH. 1990, evaluated gonadal functions in 92 male patients after treatment for advanced Hodgkin's lymphoma.[17] The patients received six to ten cycles of cyclophosphamide, vincristine, procarbazine and prednisolone chemotherapy. All patients were in remission and were followed for 1–17 years (median, 6). Testicular atrophy was noticed in 89 (96.7%) patients. All patients remained azoospermic during the period of follow-up. The testosterone levels did not differ before and after treatment. The follicle-stimulating hormone levels rose from pre-treatment values (mean ± standard deviation) of 179.27 ± 21.99–578.79 ± 102.36 ng/mL after the treatment; the rise was significant ($P < 0.001$). The abnormal rise in FSH varied in various publications in testicular tumour patients from 10% to 86%, likely due to variable post-chemotherapy intervals at which these hormone levels were measured.[17] A number of studies have shown that gonadal dysfunction is greatest immediately after chemotherapy. For instance, in a cross-sectional study, showed a higher rate of elevated LH and FSH levels in the 1st year compared to the number measured after 8 years of follow-up (LH 32% vs. 3.6%, FSH 89% vs. 64%). Derangement in FSH levels indicates the effect of cytotoxic chemotherapy on Sertoli cells. These cells with high proliferation rates are more prone to this side effect.[12]

In this study, we have not undertaken an analysis of V spermatogenesis, but a number of studies, such as have emphasised the close correlation between FSH levels and sperm counts (Brennemann *et al*., 1997; Jacobsen *et al*., 2001; Aass *et al*., 1991).[12,14,15] On this basis, the elevated level of FSH would suggest that there is a significant long-term impairment of spermatogenesis. We also studied various subgroups and noted that all the groups studied here had a statistically significant rise in post-chemotherapy FSH levels. Furthermore, at 12 weeks, the comparison in

Table 1: Comparison of mean pre-chemotherapy and 12 weeks post-chemotherapy serum hormones level of testosterones, LH, FSH and prolactin in study population.

Groups	Mean	*N*	Std. Deviation	*t*	Df	*P*-value
Testosterone pre-chemo	640.70	48	215.82	6.46	47	0.00
Testosterone 12 weeks post-chemo	460.22	48	228.62			
LH pre-chemo	4.57	48	2.10	−5.00	47	0.00
LH 12 weeks post-chemo	11.84	48	10.66			
FSH pre-chemo	3.93	48	1.35	−6.92	47	0.00
FSH 12 weeks post-chemo	16.54	48	12.79			
Prolactin pre-chemo	9.03	48	4.38	−5.62	47	0.00
Prolactin 12 weeks post-chemo	12.92	48	6.56			

LH: Luteinising hormone, FSH: Follicle-stimulating hormone, Df: Degrees of freedom

the rise in FSH levels between cisplatin, cyclophosphamide or combined cisplatin and cyclophosphamide was not statistically significant. FSH, thus, can become an indicator of the recovery from gonadal dysfunction as a derangement in FSH level is the last to recover in gonadal hormones recovery to normalisation.

LH

Overall, 25 patients had deranged LH levels post-chemotherapy, which accounts for 52.08%. This derangement is more compared to testosterone (22.91%). This suggests that even before the fall of testosterone, there was a rise in LH levels. This was much less than the patients who had shown a rise in FSH levels, that is 83.3% suggesting the resistance of LCs of the testis to the cytotoxic effects of the chemotherapy. This derangement is consistent with the following studies done earlier. LH rise had been from 2% to 86%, reflecting the blood sampling at the variable in the process of recovery of spermatogenesis interval post-chemotherapy. In a study by Kreuser *et al*. in 1989,[18] LH rise was present only in 2% of patients, and the time of sampling was 1–6 years post-chemotherapy.[18] It also showed that mean LH, testosterone and prolactin levels were within normal limits before, during and after 1–6 years of chemotherapy. Twenty per cent (4/20) of the patients revealed pathologically elevated FSH levels due to pre-treatment gonadal dysfunction. Germinal aplasia occurred in all the patients in the 1st year after chemotherapy, as 100% rendered azoospermic and 95% showed statistically significant elevated FSH values (P = 0.001). In the 3rd year after chemotherapy, 80% (8/10) of the patients showed normalisation of FSH levels and 100% (7/7) recovery of sperm production but with a high degree of immotile sperm. Although these results emphasise the restitution of spermatogenesis in the 3rd year after cessation of PVB (cisplatin, vinblastine, bleomycin) regimen, a minority of these patients fathered children, probably due to reduced sperm motility.

A study by Hansen *et al*. showed that subclinical LC dysfunction with normal testosterone and elevated LH was observed in 59% of the patients who had received chemotherapy, leading to a persistent impairment of fertility and LC function in the majority of patients with testicular tumour.[19] The median period in a study by Hansen *et al*.[19] was about 40–77 months post-chemotherapy.[10] Studied the gonadal function following chemotherapy for childhood Hodgkin's disease at a median of 6 years of diagnosis.[20] Subtle LC dysfunction was identified in 24.4% with raised LH levels. In this study, a statistically significant rise in LH levels post-chemotherapy was found in all subgroups, and there was no difference noted in the rise pattern when cisplatin only, cyclophosphamide only or cisplatin and cyclophosphamide combined chemotherapy groups were compared to each other.[20] Hence, in the initial weeks of post-chemotherapy, it can be concluded that derangement of spermatogenesis was independent of tumour type or chemotherapy type. Furthermore, it is independent of the dose of cisplatin because both low and high-dose cisplatin groups had significant derangement in the hormonal profile as compared to pre-chemotherapy.

Prolactin

Prolactin levels have been studied till now in only a few of the studies earlier. In this study, we found a significant increase in mean prolactin levels in various subgroups studied. However, the mean post-chemotherapy prolactin levels were within the normal range of the lab. All over, we had 11 patients who had elevated prolactin levels beyond the upper limit of normal, accounting for 22.92% of total patients. The implication of the rise in prolactin is difficult to explain at this stage and to establish whether it is gonadal damage sequelae or not and requires more studies correlating to chemotherapy effects. Earlier studies have shown a normal or mild rise in prolactin levels, but none could derive any conclusion based on this hormone. Still, the role of prolactin is obscure in the process of spermatogenesis or the hypothalamus-pituitary-testicular axis due to the lack of a proper *in vitro* model.

CONCLUSION

The results demonstrated a significant decline in gonadal dysfunction. Several authors have compared the patients treated with orchidectomy only. Studies have demonstrated greater testicular dysfunction in the cytotoxic treated groups; evidence of germinal epithelial damage was indicated by raised FSH concentration and reduced sperm count. In addition, mild LC impairment, as indicated by raised LH concentration, was found in 59–75% of men following chemotherapy; similar results have been obtained in cisplatin-based chemotherapy for lung cancer.

The high-dose, as well as low-dose cisplatin group was associated with significant gonadal dysfunction in testicular tumour patients, and hence, regimens using low-dose cisplatin at the cost of compromising cure rate for the motive of preservation of fertility are not warranted. There was no statistically significant difference found in alteration in mean testosterone, mean LH, or mean FSH prolactin levels among cisplatin, cyclophosphamide or combined cisplatin and cyclophosphamide group chemotherapy at least in the initial weeks of post-chemotherapy. In brief, it can be concluded that there is significant gonadal dysfunction in cancer patients receiving cytotoxic chemotherapies such as cisplatin and cyclophosphamide. Hence, it is crucial to inform the patients and their relatives about potential side effects. Despite the high percentage of chemotherapy-induced gonadal damage, prevention has received little attention to date in India. A well-functioning network of oncologists and other subspecialists needs to be augmented by increasing awareness to prevent, detect and treat expected long-term toxicities. Pre-chemotherapy cryopreservation of semen and assisted reproductive technologies are good options to describe the rate of involuntary infertility without affecting the survival of patients by decreasing doses of chemotherapy. Moreover, this study has certain limitations, such as it is very difficult to study the effect of a single chemotherapeutic drug since the patient receives multiple regimens. Semen analysis has not been carried out, as included in many earlier studies. Long-term follow-up is desired for assessments of recovery.

Ethical approval

The research/study was approved by the Institutional Ethics Committee, approval number PG Ashvini/med/2010-13.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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