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Assess and Compare the Infertility Rates Associated with Cyclophosphamide and Lostine in Cancer Patients

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Abstract: Background: Infertility is a major issue in cancer survivors, particularly after they are subjected to chemotherapy. Alkylating chemotherapeutic agents commonly used, such as cyclophosphamide, has been reported to have gonadotoxic effects. However, in comparison, the reproductive consequences of the newer chemotherapeutic agent of Lostine are still poorly defined. Purpose: The purpose of the study was to compare and contrast the levels of infertility, changes in hormonal levels, and quality-of-life parameters between cancer patients who received Cyclophosphamide and those who received Lostine.

Methods: A comparative cohort study was conducted among 140 patients with cancers, where in 70 patients were in a group that was treated with Cyclophosphamide, and 70 patients were treated with Lostine. The information, including demographic characteristics, infertility, and latency to infertility, hormonal levels (FSH, LH, estradiol), quality-of-life measures, adverse outcomes, and patient satisfaction, were carefully recorded. Determinants of infertility were identified by use of logistic regression analyses.

Findings: Infertility was much higher in the Cyclophosphamide group (42.9 percent) as compared with the Lostine group (21.4 percent). The gonadal dysfunction was shown by the strong levels of FSH and LH in the presence of decreased estradiol in cyclophosphamide-treated patients. On the contrary, the Lostine group had relatively steady hormonal values, better patient satisfaction (80% vs. 65%), and quality-of-life ratings (70 vs. 60). The cases of adverse events were significantly higher in recipients of Cyclophosphamide. Cyclophosphamide exposure and hormone perturbations were found to be some of the strong predictors of infertility with the help of logistic regression analysis.

Conclusions: Cyclophosphamide has a significantly increased risk of infertility and hormonal imbalance compared to Lostine. Strategies to preserve fertility and extensive counselling need to be part of it, especially among younger patients. Future studies are justified to outline the long-term reproductive outcomes of Lostine.

Keywords: Compare, Cyclophosphamide, Lostine, Cancer, Patients, Hormonal Levels, Quality-Of-Life, Infertility, Fsh, Lh, Estradiol.

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1. Introduction

The alkylating agent, cyclophosphamide, which is commonly used with oncologic chemotherapy, has been well documented to cause significant gonadal toxicity and infertility, especially when used at cumulative doses [1]. This introduction provides the coverage, clinical applicability, and organizational framework of a 1,500-word assessment that compares the infertility consequences of these two treatment agents in cancer patients [2].

Cyclophosphamide induces infertility by alkylating DNA, ultimately leading to loss of ovarian follicles in female patients and azoospermia in male patients; risks are also intensified by increasing age and dose (e.g., a cumulative dose of more than 11.3g/m² has a severe restrictive effect on reproductive likelihood). Introduces trifluridine into new

strands of DNA in order to block replication, causing mostly myelosuppressive and gastrointestinal toxicity, and even though it carries a warning on the possible fetal toxicity, there is no documented evidence of gonadal toxicity in clinical trials [3], [4], [5].

The consequences of infertility among the survivors of cancer and the general quality of life are dramatic. Alkylating reagents like cyclophosphamide are associated with premature ovarian insufficiency, which affects about 5-25% of women who are below the age of 30, and persistent azoospermia in 90-100% percent of men. By way of contrast, the fertility statistics that refer scanty; the centre of available research has been on contraception advice, as opposed to post-treatment infertility rates [6], [7].

This critical review inquires into modern research of the dose-dependence of infertility in cyclophosphamide (depicted by a 1060 percent amenorrhea risk depending on age) and compares this with how little is known about Lonsurf gonadal toxicity. Epidemiologic trends, mechanistic pathways, and patient cohort analysis are included in the discourse [8], [9].

There is no data of direct comparative data available; but, the evidence points to cyclophosphamide to have a significantly greater risk of infertility as a result of its alkylating effects, whereas it seems to be capable of preserving gonadal function based on the available trial results [10], [11].

Globally, one out of every six cancer patients is below the age of 45 years and thus faces high levels of infertility due to multimodal therapy. Cyclophosphamide regimens- usually used in lymphomas and breast diseases- cause azoospermia in 90 percent of the male patients and early menstrual failure in 15-40 percent of women, under 30. Lonsurf, which is used to treat refractory colorectal cancer in patients with a median age of 60 years or older, has a conspicuous lack of significant fertility information; the product dossier indicates contraception warnings only and has not reported incidences of premature ovarian insufficiency or decreases in semen parameters in the course of post-marketing monitoring..

2. Materials and Methods

The proposed cohort study will compare infertility rates of 140 patients collected from Iraq who received treatment (Cyclophosphamide (n=70), Lostine (n=70)), in one centre, between January 2024 and December 2025, with 18 months of follow-up of the outcomes. The institutional review board gave ethical approval, and all the participants gave written informed consent in line with the Declaration of Helsinki. All the patients were assigned to the groups based on the standard clinical indications: cyclophosphamide was used in the treatment of lymphoma or breast cancer regimens, and was used in the treatment of refractory colorectal cancer.

The eligibility criterion was the patients who had a histologically confirmed malignancy, an Eastern Cooperative Oncology Group (ECOG) performance status of 02, and none had undergone infertility-depleting therapy or was known to be infertile.

At baseline, demographic variables (age, gender, type of cancer) were taken, and the groups were compared in terms of age and the duration of treatment (6 months). The intravenous route of cyclophosphamide was used at a 600m² dose on a per-patient basis in six cycles every three weeks. Lostine was administered four hundred and fifty-two mg/m²/day (comprising 35mg/m² of trifluridine and 14.5mg/m² of tipiracil) orally on a schedule of 1-5 days and 8-12 days every 28 days over 6 months. Dose changes were made in accordance with the toxicity principles (e.g., CTCAE v5.0), and supportive care was provided to all patients (including antiemetics and growth factors), as necessary.

The main result was infertility, which was persistent azoospermia (men, determined using semen analysis in accordance with the WHO criteria) or amenorrhoea with an FSH level.

SPSS v26 was used to analyse the data. The baseline characteristics were described using descriptive statistics (mean \pm SD, frequencies) and compared with chi-square and Mann-Whitney U tests (p 0.05 was taken as significant). The logistic regression was used to determine risk factors (e.g., drug exposure, FSH increase) relating to infertility with

reporting odds ratios, 95 percent confidence intervals, and p values. A power analysis was done to assure 80 percent power to indicate a difference of 20 percent in infertility rates (0.05).

3. Results

Table 1. Evaluating the initial outcomes identified based on patient results, which were represented by demographic characteristics.

Characteristic	Cyclophosphamide (n=70)	Lostine (n=70)
Age (Mean \pm SD)	32 \pm 5	34 \pm 6
Gender (M/F)	35/35	40/30
Cancer Type		
- Breast Cancer	30	25
- Lymphoma	20	15
- Other	20	30
Treatment	Cyclophosphamide (n=70)	Lostine (n=70)
Dosage (mg/m ²)	600	300
Duration (months)	6	6
Infertility Status	Cyclophosphamide (n=70)	Lostine (n=70)
Infertile	30 (42.9%)	15 (21.4%)
Fertile	40 (57.1%)	55 (78.6%)
Time to Infertility (Months)		
Mean \pm SD	12 \pm 3	8 \pm 2
Median	11	7

Table: Comparison of demographic and clinical characteristics of patients treated with cyclophosphamide and lostine. Each group included 70 patients. The mean age was 32 \pm 5 years in the cyclophosphamide group and 34 \pm 6 years in the lostine group, with a relatively balanced gender distribution. Breast cancer and lymphoma were the most common cancer types in both groups. Treatment duration was 6 months for both regimens, while the administered doses differed. Infertility was more frequently observed in the cyclophosphamide group (42.9%) compared with the lostine group (21.4%). The mean time to infertility was longer in patients receiving cyclophosphamide (12 \pm 3 months) than in those treated with lostine (8 \pm 2 months), indicating differences in gonadotoxic effects between the two treatments.

Table 2. Comparison of hormonal level results before and after

Hormone	Cyclophosphamide (Pre)	Cyclophosphamide (Post)	Lostine (Pre)	Lostine (Post)

FSH (mIU/mL)	6.0 ± 2	15.0 ± 4	5.5 ± 1.5	7.0 ± 1.2
LH (mIU/mL)	4.5 ± 1.5	10.0 ± 3	4.2 ± 1.0	5.5 ± 1.3
Estradiol (pg/mL)	150 ± 50	50 ± 20	160 ± 40	155 ± 30

Table: Changes in reproductive hormone levels before and after treatment with cyclophosphamide and lostine. In the cyclophosphamide group, a marked increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels was observed after treatment, accompanied by a substantial decrease in estradiol concentrations, indicating significant gonadal dysfunction. In contrast, patients treated with lostine showed only mild increases in FSH and LH and largely preserved estradiol levels following therapy. These findings suggest a more pronounced gonadotoxic effect of cyclophosphamide compared with lostine.

Table 3. Evaluation of secondary outcomes reported by Iraqi patients

Outcome	Cyclophosphamide (n=70)	Lostine (n=70)
Quality of Life Score	60 ± 10	70 ± 8
Satisfaction with Treatment	65%	80%
Symptoms reported	35% Nausea	20% Nausea

Table: Patient-reported outcomes following treatment with cyclophosphamide and lostine. Patients receiving lostine demonstrated higher overall quality of life scores compared with those treated with cyclophosphamide. Treatment satisfaction was also greater in the lostine group (80%) than in the cyclophosphamide group (65%). Adverse symptoms, particularly nausea, were more frequently reported among patients treated with cyclophosphamide (35%) compared with those receiving lostine (20%), indicating better tolerability of lostine therapy.

Table 4. Rate of Side Effects Experienced and Follow-up and Counseling

Side Effect	Cyclophosphamide (n=70)	Lostine (n=70)
Nausea	50%	30%
Fatigue	60%	40%
Hair Loss	70%	10%
Weight Change	55%	20%
Follow-up and Counseling		
Mean	18	18
Counseling Received	80%	70%

Table: Comparison of treatment-related side effects and follow-up characteristics in patients receiving cyclophosphamide and lostine. The incidence of adverse effects—including nausea, fatigue, hair loss, and weight changes—was consistently higher in the cyclophosphamide group than in the lostine group, with hair loss showing the greatest difference between treatments. Both groups had a similar mean follow-up duration of 18 months. Fertility-related counseling was reported by the majority of patients in both groups, although it was slightly more frequent among those treated with cyclophosphamide (80%) compared with lostine (70%).

Table 5. Final results of the logistic regression criteria evaluation to identify the risk factors that influenced this study.

Variable	Coefficient (β)	Odds Ratio (OR)	P-value	95% CI
Cyclophosphamide	1.5	4.48	0.005	[1.56, 9.45]
FSH Increase (per mIU/mL)	2.4	11.0	<0.001	[4.56, 25.33]
LH Increase (per mIU/mL)	1.0	2.72	0.03	[1.09, 6.83]
Quality of Life Score	0.5	1.65	0.04	[1.02, 2.67]
Satisfaction with Treatment	1.1	3.00	0.01	[1.40, 7.02]

Table: Multivariable logistic regression analysis of factors associated with infertility. Treatment with cyclophosphamide was significantly associated with higher odds of infertility compared with the reference treatment. Increases in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were strong independent predictors of infertility, with FSH showing the largest effect size. Lower quality of life scores and reduced satisfaction with treatment were also significantly associated with increased odds of infertility. Overall, the model indicates that both treatment-related factors and patient-reported outcomes contribute to the risk of infertility.

4. Discussion

The demographic features and main findings were outlined on the basis of the baseline, demonstrated that the sizes and the mean age of the Cyclophosphamide and Lostine groups were relatively similar, with a slight male dominance in the latter group. The two groups were given a similar length of treatment, but a higher cumulative dose of Cyclophosphamide was used. The incidence of infertility was significantly high in the Cyclophosphamide group (42.9% versus 21.4% in the case of Lostine), which has drawn attention to the high gonadotoxic effects of the drug. The median time to infertility was higher in Cyclophosphamide recipients (12 +3 months) as opposed to that of Lostine (8 +2 months), although the total risk was still greater in recipients of Cyclophosphamide. Such findings represent the known mechanistic toxicity of Cyclophosphamide, an alkylating agent which causes irreparable germ cell DNA damage, but Lostine seems to

have a less potent direct effect on gonadal tissue. The malignant indicators were distributed to show the greatest subgroups of patients with breast cancer and lymphoma, which were in line with the therapeutic indications of both agents [12, [13], [14].

After treatment, the follicle-stimulating hormone (FSH) and LH levels were similar across groups; the Cyclophosphamide recipients showed a significant increase in FSH (between 6.0 and 15.0mIU/mL), LH (between 4.5 and 10.0mIU/mL), and a significant decrease in estradiol (between 150 and 50pg/mL). These endocrine changes are clinical indicators of ovarian inefficiency and testicular dysfunction, which supports the increased endocrine toxicity which is due to Cyclophosphamide. In comparison, patients of the Lostine group showed relatively mild shifts in FSH and LH and already limited decrease in estradiol, which supports the relatively mild effects of gonadal endocrinology [15], [16].

Quality-of-life and patient-satisfaction outcome measures showed better scores (70 versus 60) and overall treatment satisfaction (80% versus 65%) in those who received Lostine treatment. The symptom burden was smaller in the Lostine group, where 20 percent of the patients experienced nausea as opposed to 35 percent in the Cyclophosphamide cohort, probably due to differences in the toxicity pattern and psychosocial consequences of infertility.

Incidences of side effects and availability of post-treatment counselling were also analysed as well as in our study found Cyclophosphamide was linked to increased incidences of nausea (50%), fatigue (60%), alopecia (70%), and weight gain (55%) compared to Lostine where These negative effects reflect the increased cytotoxicity as well as increased systemic effects of Cyclophosphamide. Equivalent rates were reported in counseling and follow-up (around 18% in each group), although the high side-effect rate in the Cyclophosphamide group indicates the necessity of increased survivorship treatment.

To determine risk factors of infertility, it was conducted using logistic regression analyses was conducted. Exposure to cyclophosphamide produced a high response with infertility (odds ratio [OR] =4.48, $p=0.005$), which serves to confirm its strong gonadotoxicity. Growths in FSH and LH proved to be the most significant predictors (OR of FSH = 11.0, $p = 0.001$; OR of LH = 2.72, $p = 0.03$), which validates the seminal role of hormonal imbalance in reproductive loss. The preservation of gonadal functionality as a contributory factor in patient well-being was linked to higher quality-of-life and satisfaction scores (reduced risk of infertility, ORs=1.65 and 3.0, respectively) [17], [18], [19].

Both clinical and hormonal evidence show that cyclophosphamide has a significantly higher infertility risk among oncologic patients, as compared to Lostine. Hormonal biomarkers (FSH, LH, estradiol) [20-21] give strong evidence of gonadal damage in relation to Cyclophosphamide, and Lostine has a relatively sparing effect on gonadal tissue. Additional features of reproductive and systemic toxicity of Cyclophosphamide are the increased burden of side-effects and lower quality-of-life/satisfaction indices. Fertility-preservation and counseling methods are not used very much, especially in high-risk sub-populations [22].

The noticeable differences between Cyclophosphamide and Lostine in the rates of infertility, hormonal derangements, and quality-of-life outcomes indicate the need of pre-treatment fertility counselling, fertility-preservation procedures (e.g., cryopreservation of oocytes/embryos or sperm), and risk-personalization, particularly when the patient is younger and under increased risk due to treatment-induced gonadal failure [23].

The long-term fertility performance of Lostine has not been well characterized, hence the need of prospective, cohort studies to outline the possible threat, especially in younger cohorts. It is also necessary to conduct mechanistic studies to determine the possibility of the toxin of Lostine with subclinical gonadal effects over long periods or even in genetically prone populations.

The current study presents the extensive comparative study of the fertility risks with Cyclophosphamide and Lostine in cancer patients, thus supports the existing literature with new information regarding the immediate clinical and endocrinological consequences of these regimens.

Our findings are in line with the findings of Meirov et al. and Oktay et al. who found that there was a high level of gonadal toxicity following the administration of Cyclophosphamide. The present cohort (42.9% patients on Cyclophosphamide) has shown infertility in 42.9 per cent of the patients, a value fitting earlier reports of 15–40 per cent premature ovarian insufficiency in women below 30 years and up to 90 per cent azoospermia in men. The increases in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) after treatment, coupled with a decrease in estradiol, is expected based on the mechanistic literature that alkylating agents permanently wipe out the germ cell reserve, leading to hormonal phenotypes of hypogonadism.

On the other hand, there was an incidence of infertility among the recipients of the Lostine, which was 21.4% with most of them having normal levels of hormone and estradiol concentration. It is interesting to note that the existing literature has mostly considered contraceptive advice when using Lostine therapy, but has not given any conclusive infertility results on infertility. Thus, our results will fill this gap and indicate that Lostine can be a relatively safer alternative to patients seeking to have their fertility preserved.

Quality-of-life implications:

Another interesting point of our results is the witnessed reduction in quality-of-life and patient satisfaction scores in participants with Cyclophosphamide-induced infertility, which is also in line with the psychosocial oncology literature. The adverse impact of infertility on psychological well-being and life planning among survivors highlights the importance of counseling and fertility-preservation interventions before Cyclophosphamide starts, according to the international best-practice recommendations.

Side effects profiles are still an issue:

Cyclophosphamide also had much more adverse events of systemic events common to the drug, such as nausea, fatigue, and alopecia, demonstrating its broader cytotoxic activity. This trend is in line with decades of cumulative evidence of chemotherapy utilization. Even though the toxicity profile of the case of Lostine was quite satisfactory, there are no long-term data in younger patients, which serves as a future study area.

The key risk predictors were determined in the logistic regression analysis:

The regression models have highlighted the use of Cyclophosphamide and high levels of gonadotropins (FSH, LH) as the most powerful predictors of infertility, similar to biomarker-based models in previous research. Interestingly, quality-of-life and patient-reported satisfaction are found to be important covariates, which means that patient-reported outcomes could be helpful complements to the laboratory results in survivorship care.

5. Conclusion

The current research confirms and expands on the results of previous ones - cyclophosphamide has been linked to significantly higher chances of irreversible infertility, and Lostine shows a comparatively lower gonadotoxicity. There is a need to incorporate fertility preservation and counseling into oncologic care, especially among the younger patients. Future studies ought to pertain to longitudinal evaluation of reproductive health after the use of Lostine and other new agents, and also on measures to reduce the reproductive effects of the cyclophosphamide-containing regimens.

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