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ORIGINAL PAPER

Treatment with Hippo/YAP pathway modulators partially improves testicular and sperm phenotypes following cisplatin stimulation

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Summary *Background: Treatment with chemotherapeutic agents often causes side effects in male reproductive organs, which may lead to infertility. Identification of molecular targets to alleviate this effect is important to reduce the long-term effects of chemotherapeutic drugs on the reproductive capacity. In this study, we evaluated the effects of pharmacological targeting of the Hippo pathway on the male reproductive system following chemotherapeutic treatment with cisplatin.*
Materials and methods: This is a experimental study used 12 weeks old male Balb/c mice, divided into four groups.
We observed significant reduction in the numbers of spermatocytes, spermatids, Sertoli cells, and Leydig cells in the testes following cisplatin treatment. We then used two different types of Hippo pathway modulators to treat cisplatin-induced testicular and sperm phenotypes: i) XMU-MP-1, which is a strong inhibitor of mammalian sterile 20-like kinase 1/2, and ii) TT-10, which stimulates yes-associated protein (YAP) activity. We performed the analysis using the GraphPad Prism software. If the data were regularly distributed, we would compare the means of the two groups using a parametric test called the Student's t-test. A non-parametric test (Mann-Whitney U test) was employed if the data were not regularly distributed.
Results: We found that treatment with XMU-MP-1 significantly increased Leydig cell numbers. However, there was no change in sperm phenotype despite a significant improvement in sperm motility. In contrast, TT-10 treatment improved sperm concentration and morphology, and increased Leydig cell number.
Conclusions: Our data suggest that pharmacological modulation of the Hippo/YAP pathway may improve sperm and testicular phenotypes in mice following treatment with chemotherapeutic agents, such as cisplatin.

KEY WORDS: *Chemotherapy; Cisplatin; Hippo pathway; Male infertility sperm; Testis; Reproductive health.*

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INTRODUCTION

Chemotherapy is frequently used to treat cancers, including pediatric tumors such as osteosarcoma, neuroblastoma, and germ cell tumors. Chemotherapy may improve patient survival; however, it may also cause adverse effects on other organs, including the male and female reproductive systems (reviewed in *Dohle*, 2010) (1). The side effects caused on the reproductive systems may result in infertility later in life (2). Study by *Ismail et al.* (2023) reported exposure to cisplatin resulted in testicular tissue damage accompanied by decreased serum testosterone concentrations and a lower number of epididymal sperm oxidants (3).

Cisplatin is a commonly used chemotherapeutic agent. Cisplatin works by binding to DNA, especially purine bases, followed by DNA cleavage and interference with DNA repair mechanisms, eventually causing DNA damage. These processes lead to the inhibition of cell division and induction of apoptosis (4). Cisplatin can induce damage to several organs, including the liver, heart, kidneys, and testes (5). Damage to the testes may disrupt spermatogenesis and steroidogenesis (6).

Modulation of signaling pathways that are important for the regulation of cell growth and proliferation may be a possible strategy for repairing damage to the testes following chemotherapy. The Hippo signaling pathway plays a major role in mediating cell proliferation (7). The core components of the Hippo pathway control the dynamic localization of *yes-associated protein* (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) between the nucleus and cytoplasm. When the Hippo pathway is inactive, YAP/TAZ is dephosphorylated and accumulates in the nucleus, where it binds to TEA domain transcription factor (TEAD) and other transcription factors to induce gene transcription (8). However, when this pathway is activated, the large tumor suppressor kinase (LATS) phosphorylates YAP/TAZ, resulting in its retention, cytoplasmic degradation, and deactivation of its co-transcriptional activity (9).

Several studies have shown that the Hippo/YAP pathway regulates important functions in the testis. For example, *Levasseur et al.* showed that YAP and TAZ regulate the expression of sex differentiation markers in mouse testes (10). Other studies have demonstrated that the Hippo/YAP pathway is differentially regulated in pubertal

mouse Sertoli cells compared to infant mice. In addition, follicle stimulating hormone was found to upregulate YAP expression in the Sertoli cells of pubertal mice but not in infant mice (11).

In this study, we hypothesized that the inhibition of the Hippo pathway and/or induction of YAP activity would improve spermatogenesis following cisplatin treatment. To address this question, we conducted an in vivo study using mice that had been treated with cisplatin. We used the Hippo pathway inhibitor XMU-MP-1 and the YAP activator TT-10 to determine whether the regeneration profile of testicular cells could be improved by targeting the Hippo pathway. We selected XMU-MP-1 because it is a well-characterized, selective small-molecule inhibitor of MST1/2, the core upstream kinases of the Hippo pathway. It was first reported by *Fan et al.* (2016) to promote tissue regeneration in vivo without overt systemic toxicity, and has since been widely applied in animal studies to explore Hippo pathway modulation. Alternative Hippo pathway inhibitors remain largely experimental, with limited in vivo validation or unsuitable pharmacokinetic properties. Thus, XMU-MP-1 represents the most established and translationally relevant pharmacological tool for investigating the role of Hippo inhibition in testicular regeneration (12).

Methods

Generation of cisplatin-induced testicular toxicity in mice

We used eight 12-week-old male Balb/c mice in each group for the study. The mice were obtained from a certified supplier (*PUSVETMA, Surabaya*). The animals were housed in standardized maintenance rooms in the experimental animal research laboratory at the Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya. Rooms were maintained at 19-22°C, 40%-65% humidity with a light-dark cycle of 12 h every day. In clinical oncology, cisplatin is commonly administered in humans at doses ranging between 50-100 mg/m² intravenously every 3-4 weeks, depending on the type of cancer and combination regimen (13). To generate a model of cisplatin-induced testicular toxicity, the mice were injected with a single dose of cisplatin (*Kalbe Farma*) at 15 mg/kg body weight, intraperitoneally. Using this approach, testicular and sperm phenotypes are expected to develop within 35 days of cisplatin injection (14). The selected dose of cisplatin (15 mg/kg, i.p.) has been widely applied in rodent models to induce testicular toxicity, with previous reports demonstrating significant impairments in spermatogenesis, reduced serum testosterone levels, and histopathological damage to the seminiferous tubules within 3-5 weeks of administration (15, 16).

Treatment with modulators of Hippo/YAP pathway

Following cisplatin induction, the mice were treated with either XMU-MP-1 (*MedChemExpress*) at a dose of 1 mg/kg body weight/day, intraperitoneally, for 21 days or TT-10 (*MedKoo Biosciences*) at a dose of 3 mg/kg body weight/day administered intraperitoneally for 21 days, starting on day 5 after cisplatin injection, to coincide with the onset of testicular damage. XMU-MP-1 is a potent MST1/2 inhibitor (12), that inactivates the Hippo pathway, whereas the YAP activator TT-10 directly stimulates YAP activity (17). The selection of XMU-MP-1 and TT-10 doses was based on previous studies, with the intraperitoneal route considered the most convenient and commonly used in mice (12, 19). The control mice received equal volumes of dimethyl sulfoxide.

Sperm analysis

The mice were sacrificed 21 days after treatment with Hippo/YAP modulators. The epididymis was harvested to collect the sperm. Fat and connective tissues were separated to facilitate sperm identification and isolation. The retrieved sperms were dissolved in 1 mL of phosphate-buffered saline and left for approximately 1 min at room temperature (24-25°C). The sperms were then examined according to the standard methods described in the sixth edition of the World Health Organization laboratory manual for the examination and processing of human semen. Sperm concentration was determined by using a hemocytometer under light microscopy. Motility was evaluated by analyzing at least 200 spermatozoa per sample at ×400 magnification, categorizing them as progressive, non-progressive, or immotile, while morphology was evaluated in smears stained with Diff-Quik, as previously described (18).

Testicular histology

Testicular tissues were collected and fixed using 4% neutral-buffered formalin for 24 h. The tissues were processed using an automated processor and solidified with paraffin. Approximately, 5 µm thick tissue sections were generated using a microtome (*Leica 2125, Chicago, IL, USA*). The testicular tissues were then analyzed using an Olympus BX-41 microscope at 400× magnification from 10-12 different fields. Spermatocytes and spermatids are differentiated in H&E-stained sections based on established morphological criteria. Spermatocytes are typically identified as large cells with round or oval nuclei containing coarse chromatin, located in the middle layer of the seminiferous epithelium. Spermatids, on the other hand, are recognized as smaller cells located near the lumen, with condensed nuclei; round spermatids exhibit rounded nuclei, while elongated spermatids have condensed and elongated nuclei parallel to the lumen (19).

Statistical analysis

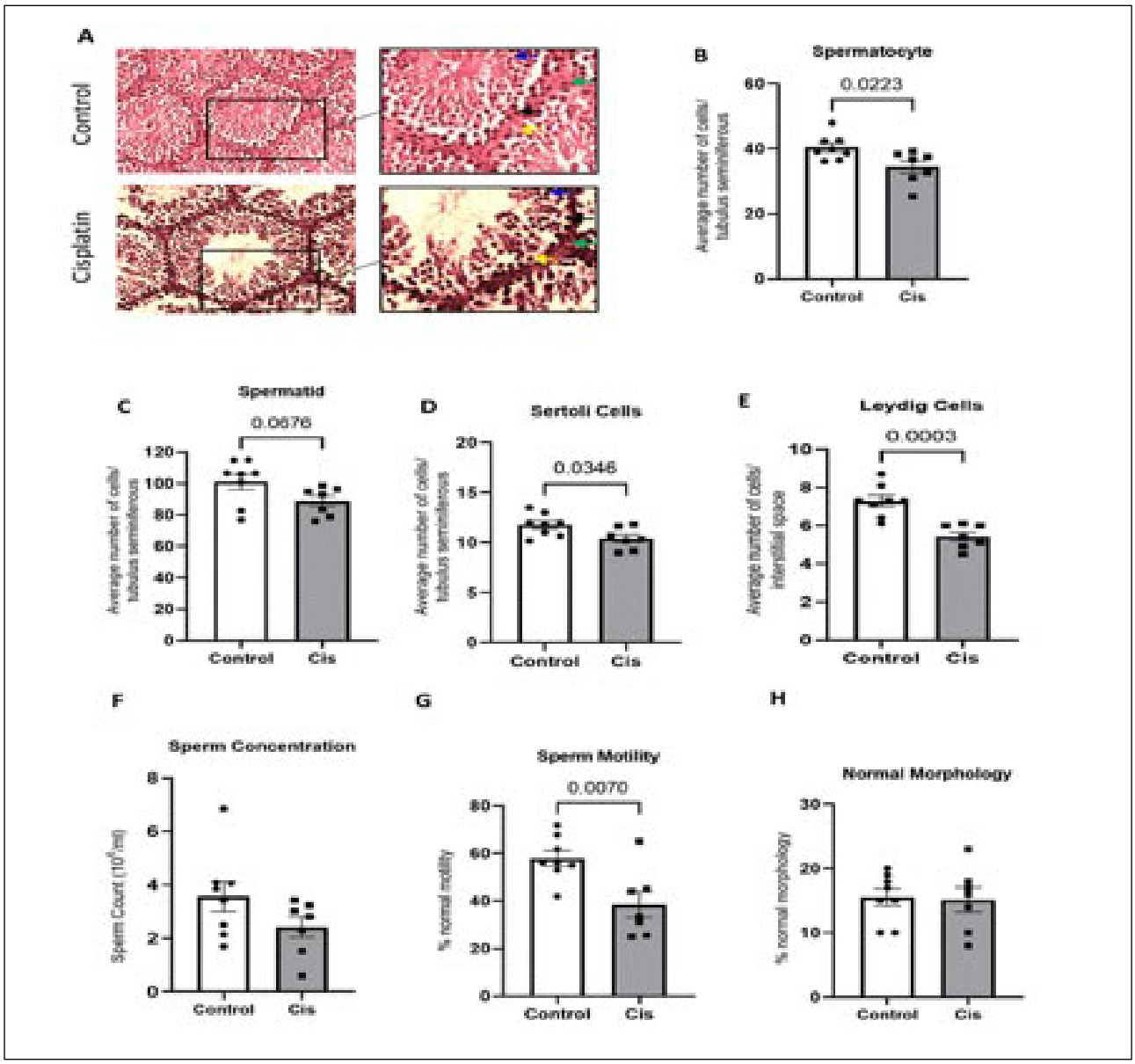
Data are presented as the mean ± standard error of the mean and were tested for normal distribution using the Shapiro-Wilk test. We used a parametric test (Student's t-test) to compare the means between the two groups if the data were normally distributed. If the data were not distributed normally, a non-parametric test (Mann-Whitney U test) was used. The results were considered statistically significant at $p < 0.05$. Statistical analyses were performed using the GraphPad Prism software (v9.5.0; *GraphPad Software, San Diego, CA, USA*).

Results

Effects of cisplatin on testicular and sperm phenotypes

To model cisplatin-induced testicular toxicity, we treated mice with a single dose of cisplatin (15 mg/kg body

Figure 1.
Effects of cisplatin treatment on testicular and sperm phenotype.
A) Representative histological sections of mouse testis following treatment with cisplatin (15 mg/ kg body weight/single dose, intraperitoneally). Testicular phenotypes were analyzed at 25 days after cisplatin injection. Cisplatin treatment significantly reduced the number of B) spermatocyte, C) spermatid, D) Sertoli cells, and E) Leydig cells. Analysis of sperm phenotypes including F) sperm concentration, G) motility and, H) morphology revealed a significant reduction in sperm motility but not sperm concentration and morphology following cisplatin treatment. (n = 7-8 in each group, numbers in the graphs indicate p values). Blue arrows indicate spermatocytes; black arrows indicate spermatogonium; yellow arrows indicate Sertoli cells; green arrows indicate Leydig cells.

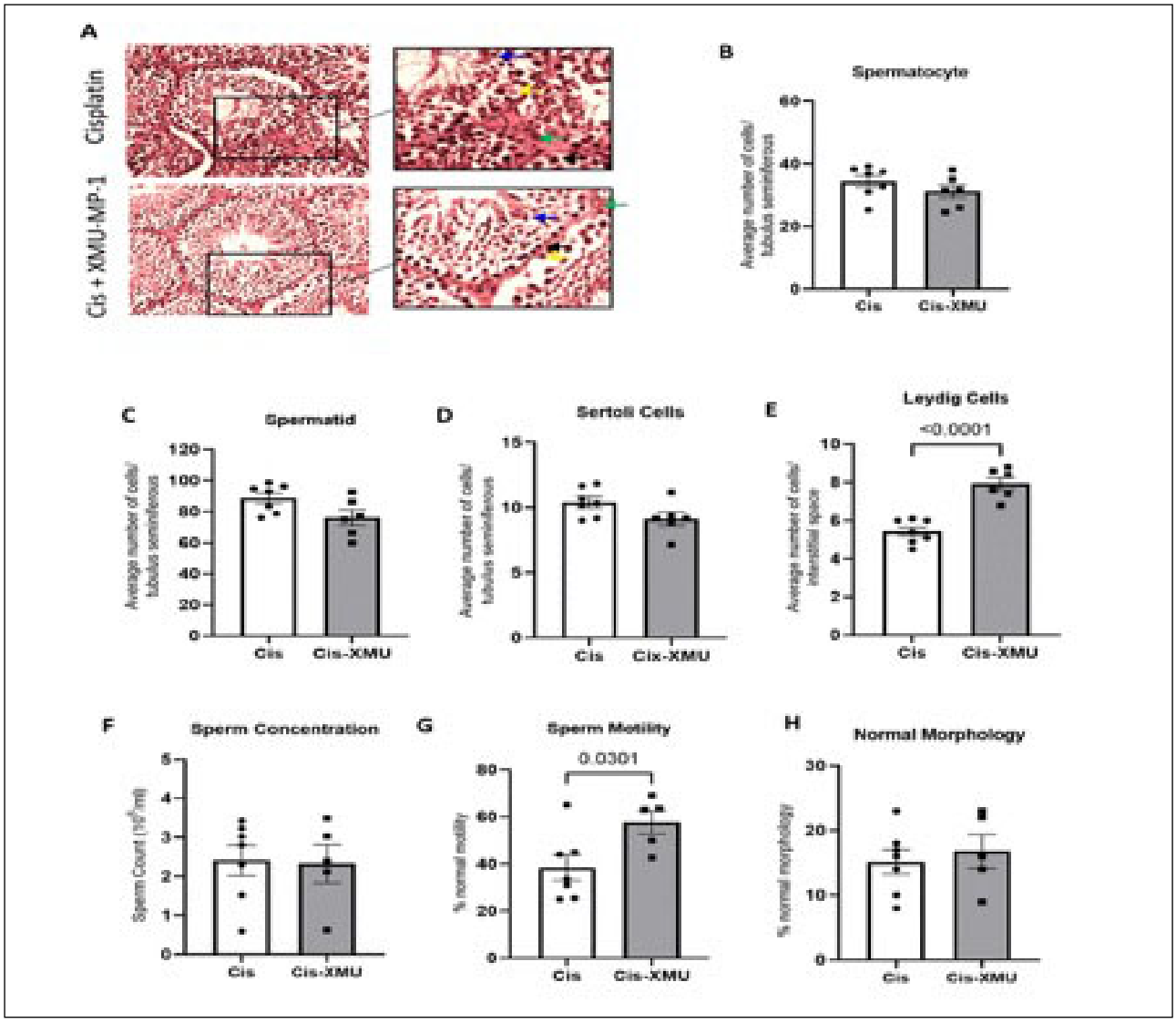


weight), intraperitoneally. The mice were sacrificed 25 days after injection, and testicular histological sections and sperm phenotypes were examined.
Analysis of testicular histology revealed a significant reduction in the number of spermatocytes, spermatids, Sertoli cells, and Leydig cells in the cisplatin-treated group (Figure 1A-E). Consistent with these findings, sperm analysis (Figure 1F-H) indicated that cisplatin treatment significantly reduced sperm motility; however, sperm concentration and morphology were not significantly affected by the treatment. Taken together, our data suggest that cisplatin adversely affects sperm and testicular phenotypes.

Treatment with the mammalian sterile 20-like kinase 1/2 (MST1/2) inhibitor (XMU-MP-1) improved Leydig cell number and sperm motility in cisplatin-treated mice

We then investigated the effects of Hippo pathway inhibition on sperm and testicular phenotypes following cis-

Figure 2.
Effects of treatment with XMU-MP-1 on testicular and sperm phenotypes of cisplatin-induced mice.
A) Representative histological sections of cisplatin-induced mouse testis following treatment with XMU-MP-1 or vehicle. XMU-MP-1 at a dose of 1 mg/kg body weight/day was administered intraperitoneally for 21 days following cisplatin injection. Testicular phenotypes including the number of B) spermatocyte, C) spermatid, D) Sertoli cells, and E) Leydig cells were analyzed. XMU-MP-1 significantly increased the number of Leydig cells. Analysis of F) sperm concentration, G) sperm motility, and H) sperm morphology were conducted in mouse sperm isolated from the epididymis. There was a significant improvement in sperm motility following XMU-MP-1 treatment. (n = 7–8 in each group, numbers in the graphs indicate p values). Blue arrows indicate spermatocytes; black arrows indicate spermatogonium; yellow arrows indicate Sertoli cells; green arrows indicate Leydig cells.

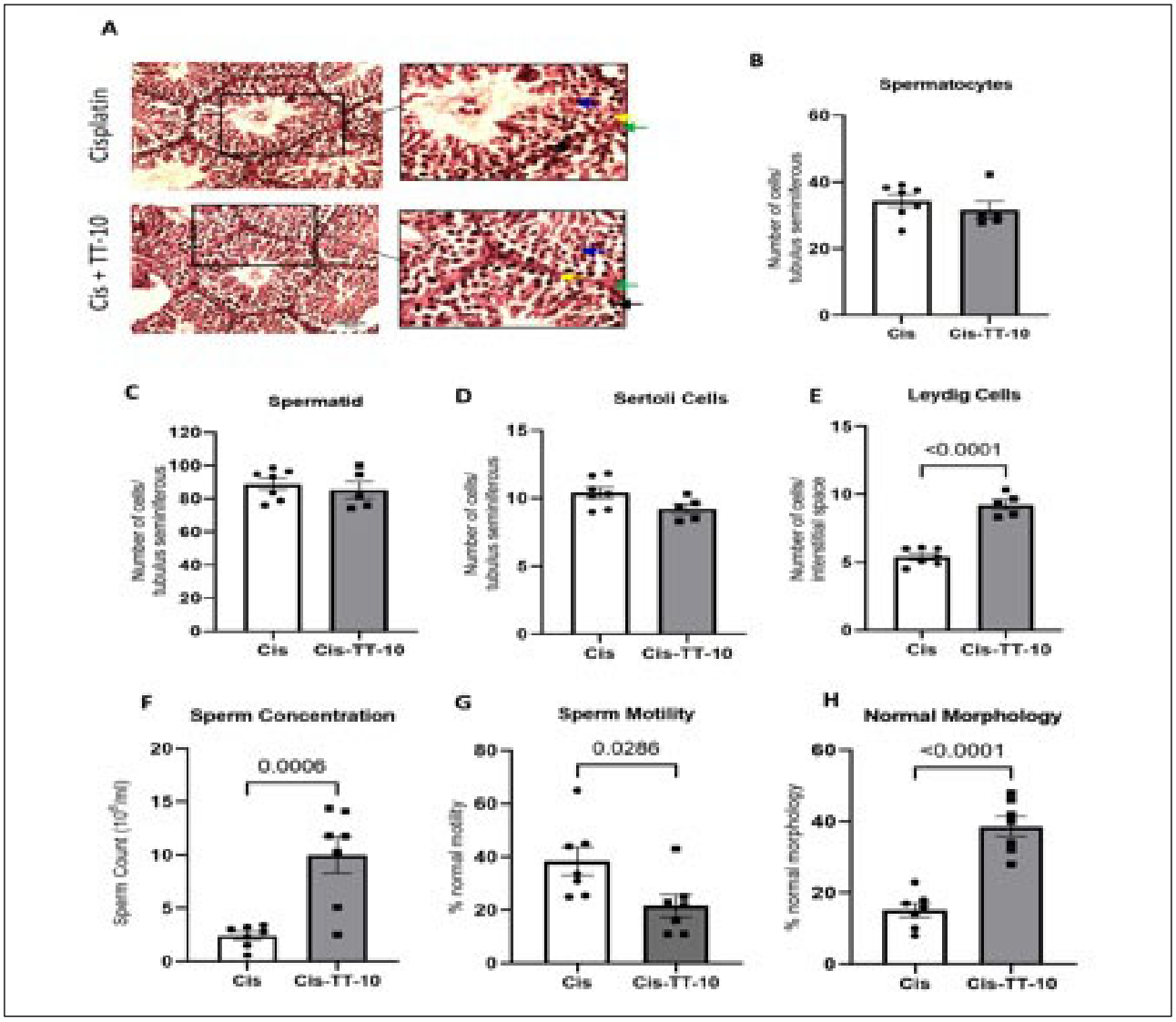


platin treatment. We used XMU-MP-1, a potent MST1/2 inhibitor (12). Inhibition of MST1/2 eventually leads to the activation of YAP, as indicated in previous studies (12, 20). Mice were treated with XMU-MP-1 (1 mg/kg body weight/day, intraperitoneally) for 21 days following cisplatin injection. The data presented in Figure 2 show that XMU-MP-1 partially corrected the sperm and testicular phenotypes of cisplatin-treated mice. We observed that Leydig cell number and sperm motility were significantly improved by XMU-MP-1 treatment. However, we did not observe any significant differences in other phenotypes, such as the number of spermatocytes, spermatids, and Sertoli cells, or sperm concentration and morphology (Figure 2B-H).

Treatment with YAP activator TT-10 improved Leydig cell number and the sperm phenotypes of cisplatin-treated mice

Next, we treated the mice with different types of Hippo pathway modulators. We used TT-10, a potent YAP activator (17). TT-10 was administered intraperitoneally at a dose of 3 mg/kg body weight/day for 21 days after cisplatin treatment. The analysis of histological sections revealed a significant increase in the number of Leydig

Figure 3.
Testicular and sperm phenotypes in mice following pharmacological modulation of YAP activity using TT-10 after cisplatin treatment.
A) Representative hematoxylin-eosin stained testicular sections of TT-10 and vehicle-treated mice following induction with cisplatin. TT-10 was administered intraperitoneally at a dose of 3 mg/kg body weight/day for 21 days following cisplatin injection. Testicular phenotypes including the number of B) spermatocyte, C) spermatid, D) Sertoli cells and, E) Leydig cells were analyzed. TT-10 treatment significantly increased the number of Leydig cells. F) Sperm concentration was significantly increased following TT-10 treatment, G) However, sperm motility was decreased after TT-10 treatment. H) The number of normal sperm morphology was significantly enhanced following TT-10 treatment. (n = 7–8 in each group, numbers in the graphs indicate p values).
Blue arrows indicate spermatocytes; black arrows indicate spermatogonium; yellow arrows indicate Sertoli cells; green arrows indicate Leydig cells.



cells. However, the analysis of Sertoli cells, spermatocyte, and spermatid counts did not show any differences between the TT-10-treated and non-TT-10-treated groups (Figure 3A-E). In terms of sperm phenotype, we observed significant improvements in sperm concentration, motility, and morphology following TT-10 treatment (Figure 3F-H).

These findings suggest that TT-10 may have a stronger effect than XMU-MP-1 in improving male reproductive organ phenotypes following chemotherapeutic treatment.

Discussion

The main finding of this study was that treatment with Hippo/YAP pathway modulators may improve sperm quality and testicular phenotypes in mice following cisplatin treatment. Cisplatin reduces sperm quality and damages the testicular morphology in rabbits (21), rats (22), and mice (22, 23). The findings of the present study are consistent with those of previous studies, as we found that cisplatin significantly decreased the number of spermatocytes, spermatids, Sertoli cells, and Leydig cells. Cisplatin treat-

ment also reduces sperm motility. Importantly, we observed that treatment with two different Hippo/YAP pathway modulators, XMU-MP-1 and TT-10, improved the sperm and testicular phenotypes following cisplatin administration. MST1/2 inhibitor (XMU-MP-1) improved sperm motility and number of Leydig cells. In contrast, TT-10, which directly activated YAP, improved all sperm parameters tested and increased the number of Leydig cells in mice exposed to cisplatin.

Cisplatin induces spermatogonial death, mainly via increased oxidative stress. This may initiate inflammation and lead to alterations in sperm chromatin integrity and DNA methylation, eventually inducing apoptosis (22, 23). Thus, decreasing reactive oxygen species levels or increasing cell regeneration appears to be a possible approach for preventing the adverse effects of cisplatin on sperm generation.

Our study demonstrated that cisplatin administration reduced sperm motility; however, it did not alter sperm morphology. This finding supports the idea that one of the main detrimental effects of cisplatin is increased *reactive oxygen species* (ROS) production (24, 25), which may interfere with sperm function and metabolism (26, 27). Increased ROS levels may have led to the decreased sperm motility. With regard to the testicular phenotype, we observed a significant reduction in the number of Leydig cells. The decrease in the number of Leydig cells may affect the production of testosterone, which is required for spermatogenesis, and thus may be related to the phenotype observed.

Notably, mature sperms are derived from the somatic cells of the seminiferous epithelium that undergo proliferation and differentiation (28); therefore, any treatment to induce sperm cell proliferation and improve the quality of sperm should target seminiferous epithelial cells.

The Hippo pathway plays essential roles in regulating cell proliferation, development, and organ size control (7). However, although the male reproductive system organ is heavily involved in germ cell division and development little is known about the role of this pathway in this organ, including the testes (11). Previous studies have reported that the Hippo pathway is expressed in the Sertoli cells of Atlantic salmon (29). Although other studies have reported the expression of YAP and TAZ in mouse testes (10), no study has evaluated the effects of pharmacological modulation of the Hippo pathway and/or YAP on sperm production and activity.

Our data showed that TT-10 might produce stronger effects on sperm phenotypes (concentration and morphology) than XMU-MP-1. Interestingly, we found consistent effects of XMU-MP-1 and TT-10 on the testicular phenotype, that is, increased Leydig cell number. Although both are considered potent YAP activators, XMU-MP-1 differs from TT-10 in its mechanism of action and target molecules. XMU-MP-1 is a kinase inhibitor that specifically binds to the ATP-binding pockets of MST1 and MST2 (12). This molecule has stronger inhibitory activity against MST2 (IC50: 38 nM) than against MST1 (IC50 71 nM) (12). XMU-MP-1 has been shown to strongly inhibit the core components of the Hippo pathway, including the inhibition of MOB1, LATS1, and YAP phosphorylation, which results in YAP nuclear translocation and activation (12, 30). It has been shown to work in several cell types, including cardiomyocytes (30), platelets (31), haematopoietic stem cells (32), and *induced pluripotent stem cells* (iPSC)-derived myocytes (33). TT-10, on the contrary, is a YAP/TAZ activator (17) and unlike XMU-MP-1, most of the reported data on the ability of TT-10 to activate YAP/TAZ have been obtained from experiments using cardiac myocytes or iPSC-derived myocytes (34, 35). Therefore, the slight differences between the effects of TT-10 and XMU-MP-1 on sperm and testicular phenotypes may be due to the different target molecules. MST1/2 may also be involved in regulating other pathways, such as Foxo1/3 (36, 37), *Akt* (38), and *Beclin1* (39). Therefore, XMU-MP-1 may modulate different signals other than Hippo/YAP, whereas TT-10 is more likely to activate YAP/TAZ only. Another possibility is the pharmacokinetics of the two molecules, particularly their ability to cross the blood-testis barrier. However, further studies are needed to understand the mechanisms by which XMU-MP-1 and TT-10 affect sperm and testicular phenotypes.

The finding that both TT-10 and XMU-MP-1 significantly increased the number of Leydig cells aligns with the idea that the Hippo signaling pathway plays an important role in the testis. Previous reports have suggested that the Hippo/YAP pathway modulates key processes during spermatogenesis. A study reported by *Zhang et al.* reported the high expression of components of the Hippo pathway in germ cells. This study also indicated a potential role for Hippo signaling in spermatogenesis in response to cytokines (40). Interestingly, in ejaculated spermatozoa, LATS1 was localized in the acrosomal head region, whereas LATS2 and YAP1 were expressed in the middle part of the sperm.

Declarations

Ethical approval and consent for participate: *This study was conducted in accordance with institutional and national research ethics guidelines and was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga (No. 136/EC/KEPK/FKUA/2021).*

Availability of data and material: *All relevant data supporting the findings of this study are included in the article. The full raw dataset is available from the corresponding author upon reasonable request.*

Competing interests: *The authors declare that they have no competing interests.*

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Authors' contributions: *ZF, JJ, CP, and MIL contributed to the conceptualization of the study. CP, BA, ZF, JJ, and MIL contributed to the methodology. CP, BA, ZF, JJ, MIL, and BH were involved in data collection and investigation. CP and BA performed the formal statistical analysis and interpretation of the data. CP, BA, and BH drafted the original manuscript. All authors contributed to the review and editing of the manuscript and approved the final submitted version.*

Acknowledgments: *None.*

This study demonstrated that LATS and YAP1 expression increases in mature sperm cells compared to that in the cauda epididymis. This finding also implies that the expression of Hippo pathway components during spermatogenesis is likely more dominant in post-testicular locations, such as the seminal and prostate vesicles, than within the testis or epididymis (40). We acknowledge that there are several limitations of this study. First, we did not examine the testosterone levels, an indicator of Leydig cell function. Since we found a significant decrease in the number of Leydig cells after cisplatin treatment, which was reversed by treatment with XMU-MP-1 or TT-10, it would be interesting to determine whether cisplatin also affected serum testosterone levels. In addition, our focus was restricted to cisplatin-induced testicular toxicity, while other chemotherapeutic agents such as cyclophosphamide, busulfan, and doxorubicin are also known to impair spermatogenesis; further studies are warranted to evaluate whether Hippo pathway modulation could similarly restore testicular function in these models. Second, understanding the possible interactions between Hippo signaling and testosterone levels is also important, as several lines of evidence have suggested that there is crosstalk between Hippo pathways and androgen signaling in the regulation of cell survival and cellular homeostasis (41, 42). Moreover, we did not directly assess the activity of downstream Hippo signaling effectors such as TAZ and TEAD, nor establish the baseline status of Hippo signaling activation following cisplatin exposure through PCR or immunoblotting.The present study did not encompass these mechanistic investigations, yet they constitute significant future directions to more fully understand how Hippo signaling regulates testicular regeneration.

Finally, other parameters, such as ROS levels, can be measured to further understand the testicular response to MST1/2 inhibitors and YAP activators. This analysis should be conducted in the future to better understand the role of the Hippo pathway in spermatogenesis and testicular physiology.

Conclusions

In conclusion, our findings suggest that modulation of the Hippo pathway, a key signaling cascade controlling cell proliferation, may contribute to improvements in sperm concentration and morphology in a mouse model treated with cisplatin. While these results provide preliminary insights into potential therapeutic strategies for chemotherapy-induced infertility, further studies involving molecular and hormonal analyses will be necessary to fully elucidate the underlying mechanisms and validate the translational potential of this approach.

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