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SHORT COMMUNICATION

Impact of Imatinib on the Fertility of Male Patients with Chronic Myelogenous Leukaemia in the Chronic Phase

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Abstract
Background Imatinib is a first-line tyrosine kinase inhibitor for treating chronic myelogenous leukaemia (CML) and has greatly improved the prognosis of this disease. An increasing number of CML patients of reproductive age are diagnosed each year, and the impact of imatinib on fertility is a major concern. Providing useful advice to these patients regarding the choice of their therapeutic treatment is very important.
Objective This study examined the impact of imatinib on the fertility of male patients with CML in the chronic phase.
Patients and Methods We performed a study of 48 adult male CML patients in the chronic phase (CML-CP), 50 healthy control subjects, and 10 male patients with infertility. Imatinib levels in semen and plasma were measured using high-performance liquid chromatography/mass spectrometry. We examined the effects of imatinib on sperm parameters and the male reproductive system using a computer-assisted sperm assay and ultrasound, respectively. We analysed sex hormone levels in the sera of CML-CP patients using an enzyme-linked immunosorbent assay.
Results Imatinib levels in semen were comparable to plasma levels in CML-CP patients. CML-CP patients treated with imatinib exhibited reduced sperm density, counts, survival rates, and activity. Ultrasound demonstrated that the shape and size of the testis and epididymis in CML-CP patients undergoing imatinib treatment were normal. However, 19 of these patients exhibited a hydrocele in their tunica vaginalis, with a large dark area of effusion (0.7–2.9 cm in width). Sex hormone levels in the sera of the CML-CP patients were normal.
Conclusions These results suggest that imatinib crosses the blood-testis barrier and reduces sperm density, sperm count, survival rates, and activity in CML-CP patients. However, imatinib did not affect the structure of reproductive organs or sex hormone levels.

Key Points

Imatinib has dramatically changed the prognosis of CML, while the impact of imatinib on fertility in male CML patients is unclear.

Imatinib can cross the blood-testis barrier and reduce sperm density, sperm count, survival rate and activity in CML-CP patients.

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1 Introduction

Chronic myelogenous leukaemia (CML) is a malignant haematopoietic stem cell disease that is characterized by

unregulated proliferation of myeloid cells in the bone marrow. A reciprocal chromosomal translocation between chromosomes 9 and 22, forming the Philadelphia (Ph) chromosome, leads to the formation of the *BCR-ABL* fusion gene, encoding the oncogenic tyrosine kinase BCR-ABL [1]. The Ph chromosome is a definitive diagnostic marker for CML, and tyrosine kinase inhibitors (TKIs) targeting BCR-ABL are used as therapeutic treatments in CML patients. Imatinib is a small-molecule TKI that inhibits BCR-ABL tyrosine kinase activity and blocks its downstream signal transduction pathways. This blockade leads to apoptosis of myeloid cells and inhibition of myeloid cell growth [2]. Imatinib is the standard treatment for CML patients because it exhibits few side effects, and it is currently used as the first-line treatment for chronic-phase CML [3]. An 8-year follow-up of the International Randomized study of Interferon versus STI571 (IRIS) demonstrated that the overall survival rate of CML patients who received imatinib treatment was 85%, and the percentage of CML patients who progressed to the advanced stage of CML was reduced by 93% [4].

CML can occur at any age, and its prevalence is higher in men than in women. Epidemiological studies demonstrated that the average onset age for CML in Asia was 38.3 years, which is lower than the average onset age worldwide [5]. A younger onset age for CML in China was also evident from data from different districts [6]. The higher survival rate of younger CML patients has significantly increased the number of CML patients of reproductive age. These patients frequently seek advice from their physicians on reproduction and conception while undergoing therapeutic treatment because of the desire for a similar quality of life to non-leukaemic individuals in respects such as fertility, pregnancy, and family planning.

The widespread use of imatinib for the treatment of CML patients has increased attention to the impact of imatinib on reproduction and conception. While successful pregnancies in female CML patients were reported, potential adverse effects of imatinib on foetal growth and development cannot be ignored because of teratogenic effects of imatinib during the first months of pregnancy. The impact of imatinib on fertility in male CML patients is a key issue to address. We investigated the effects of imatinib on the fertility of male CML patients undergoing imatinib therapy to provide CML patients with useful advice on reproduction.

2 Materials and Methods

2.1 Patients

This study was performed in male patients diagnosed with CML-CP at the 210th Hospital of PLA (Dalian, China) from January 2010 to December 2014. Two independent reviewers reviewed the medical charts and performed the data extraction. Forty-eight male CML-CP patients who received imatinib for a median of 36 (3–96) months after diagnosis were included in this study. Fifty healthy volunteers in the outpatient department during the same period were included as normal controls, and 10 patients with male infertility in the reproductive centre of the outpatient department were included as positive controls. All participants participated in this study voluntarily. The ages of all participants were between 15 and 51 years. The median ages of participants in the CML-CP group, normal control group, and positive control group (patients with male infertility) were 34.2 ± 7.0, 38.5 ± 10.1, and 28.4 ± 6.2 years, respectively.

2.2 Ethics Statement

The 210th Hospital of PLA, China, approved this study. All patient data were handled and de-identified according to ethical and legal standards. Written informed consent was obtained from all participants involved in the study.

2.3 Inclusion Criteria

CML-CP was diagnosed according to the revised 2011 China CML Diagnostic Criteria, as well as the National Comprehensive Cancer Network and European Leukaemia Net (ELN) guidelines. Examination results included at least one positive result for the Ph chromosome or BCR-ABL fusion protein, as well as a CML-compatible myelogram and blood cell examination. All male CML patients were between 15 and 51 years old without male reproductive system disorders. All CML patients received oral imatinib treatment at a dose of 400 mg/day.

2.4 Evaluation of Fertility

Ultrasound examination was performed to evaluate the male reproductive system, and the mean values of colour Doppler ultrasonography were analysed. Semen samples were collected and liquefied after incubation at room temperature (no less than 22 °C) for up to 1 h. Semen specimens were evaluated for basic parameters in an on-site laboratory using a computer-assisted sperm assay (CASA).

2.5 Ultra-Flow Liquid Chromatography-Mass Spectrometry (UFLC-MS)

Peripheral blood plasma samples of CML-CP patients were collected and stored at −20 °C. Semen (2 mL) was drawn from each CML-CP subject in heparin-containing tubes and centrifuged within 30 min of sample collection at a speed of 5000 g for 10 min. Imatinib concentrations were analysed using an UFLC-MS system (UFLC LC20AD, Shimadzu, Japan; QTRAP4500, ABSCIEX, Framingham, MA, USA).

Chromatographic separation was performed using a CAPCELLPAK-C18 column (2.0 × 100 mm, 5-μm particle size; Shiseido, Tokyo, Japan). The mobile phase was composed of deionized water containing 2 mM ammonium acetate and 0.05% trifluoroacetic acid (TFA) in water (solvent A) and 0.05% TFA in MeOH/acetonitrile (1:1, *V*/V) (solvent B) at a flow rate of 0.1 mL/min. Mass spectrometry detection was performed in positive mode using the total eluent from the chromatographic system, i.e., without splitting. The total runtime was 5.5 min. The electrospray interface was maintained at 250 °C. Nitrogen nebulization was performed at a nitrogen flow rate of 15 L/min. The data were captured in Analyst 1.6.2 software (ABSCIEX, Framingham, MA, USA).

2.6 Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA was performed to detect sex hormone levels (Immunlite2000, Siemens Medical Solutions Diagnostics, Deerfield, IL, USA), following the manufacturer's procedures. Sex hormone levels, including follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol (E2), progesterone (P), testosterone (T), and prolactin (PRL), were measured in patient sera.

2.7 Statistical Analysis

The data are presented as the mean. Statistical significance was analysed using ANOVA, followed by a least significant difference post hoc test, using SPSS 13.0 software (SPSS, USA). *P* values less than 0.05 were considered statistically significant.

3 Results

3.1 Imatinib Was Detected in the Semen and Plasma of CML-CP Patients Receiving Imatinib Treatment

We analysed imatinib concentrations in the plasma of 48 CML-CP patients using an UFLC-MS system. The average imatinib concentration was 1524.14 ± 461.52 ng/mL. We also evaluated imatinib levels in the semen of 11 CML-CP patients to determine whether imatinib crosses the blood-testis barrier and could potentially impact fertility. Imatinib levels in the plasma and semen were 1471.184 ± 569.65 ng/mL and 1397.27 ± 424.83 ng/mL, respectively, in the 11 patients. These results demonstrated the presence of imatinib in the semen of CML-CP patients, and drug levels in semen were comparable to plasma levels in these patients.

3.2 Imatinib Treatment Reduced Sperm Survival and Activity in CML-CP Patients

We compared the sperm count and survival rate in CML-CP patients receiving imatinib with those in healthy controls and patients with male infertility to examine whether imatinib treatment altered sperm quality and quantity in CML-CP patients. The results demonstrated that sperm density (53.11 vs. 119.74 × 10^6/ml), count (132.86 vs. 406.88 × 10^6), survival rate (61.97 vs. 79.22%), and activity (48.27 vs. 67.32%) in CML-CP patients receiving imatinib were significantly lower than those in healthy control individuals. However, these numbers were higher than those in patients with male infertility (Table 1).

3.3 The Effects of Imatinib on Male Reproductive Structures and Functions in CML-CP Patients

We examined male reproductive structures and functions to assess further the impact of imatinib on the reproductive system. Ultrasound examination revealed that the shapes and sizes of the testis and epididymis of CML-CP patients were normal and not significantly different from those of healthy control individuals. The shapes and sizes of the testis and epididymis of patients with male infertility were also similar to those of healthy control individuals (Table 2). However, hydrocele was found in the tunica vaginalis of 19 of the 48 CML-CP patients receiving imatinib treatment, with a larger dark area of effusion (0.7–2.9 cm in width) compared with

Table 1 Reduced sperm survival and activity in CML-CP patients receiving imatinib treatment

Parameter	CML-CP Group (n = 48)	Normal Control Group (n = 50)	Infertility Group (n = 10)
Sperm Density(×10^6/ml)	53.11 ± 34.23$^{**\,\Delta\Delta}$	119.74 ± 56.95$^{\Delta}$	14.45 ± 3.14**
Total Sperm Count(×10^6)	132.86 ± 99.41$^{**\Delta}$	406.88 ± 159.62$^{\Delta\Delta}$	41.23 ± 19.62**
Sperm Survival Rate (%)	61.97 ± 11.61$^{**\Delta}$	79.22 ± 21.27$^{\Delta\Delta}$	31.13 ± 6.77**
Sperm Activity Level [a] (%)	26.24 ± 10.21$^{**\Delta}$	36.49 ± 15.01$^{\Delta}$	7.40 ± 6.57**
Sperm Activity Level[b](%)	27.03 ± 4.37$^{**\Delta}$	30.84 ± 11.66$^{\Delta}$	14.96 ± 5.33**
Sperm Activity Level [a+b](%)	48.27 ± 12.96$^{**\Delta}$	67.32 ± 16.89$^{\Delta}$	22.35 ± 24.92**

Sperm Activity Level [a, b, a+b], the judgement criteria for sperm activity are shown [7] as the mean ± SD, $^{**}p < 0.01$ vs. the normal control group, $^{\Delta}p < 0.05$ vs. the infertility group, $^{\Delta\Delta}p < 0.01$ vs. the infertility group

Table 2 Characterization of the male reproductive system

Parameters		CML-CP Group (n = 48)	Normal Control Group (n = 50)	Infertility Group (n = 10)
Testis Length (cm)	Left	2.77 ± 0.31	3.23 ± 0.25	3.23 ± 0.48
	Right	3.27 ± 0.23	3.13 ± 0.54	3.16 ± 0.57
Testis Width (cm)	Left	1.87 ± 0.30	2.17 ± 0.15	1.98 ± 0.43
	Right	1.97 ± 0.43	2.15 ± 0.33	2.07 ± 0.20
Testis Height (cm)	Left	2.55 ± 0.58	3.17 ± 0.93	2.57 ± 0.41
	Right	3.02 ± 0.43	2.72 ± 0.19	3.03 ± 0.43
Epididymis Length (cm)	Left	0.83 ± 0.15	0.70 ± 0.15	0.68 ± 0.26
	Right	0.88 ± 0.17	0.70 ± 0.21	0.76 ± 0.19
Epididymis Width (cm)	Left	0.33 ± 0.08	0.28 ± 0.04	0.38 ± 0.10
	Right	0.37 ± 0.08	0.38 ± 0.12	0.38 ± 0.12
Epididymis Height (cm)	Left	0.80 ± 0.08	0.78 ± 0.22	0.72 ± 0.19
	Right	0.93 ± 0.27	0.96 ± 0.28	0.80 ± 0.28
Dark Area of effusion (cm)	Left	$1.43 \pm 0.80^{**\Delta\Delta}$	0.28 ± 0.41	0.13 ± 0.24
	Right	$1.61 \pm 0.86^{**\Delta\Delta}$	0.28 ± 0.37	0.11 ± 0.18

The data are shown as the mean ± SD, $^{**}p < 0.01$ vs. the normal control group, $^{\Delta\Delta}p < 0.01$ vs. the infertility group

that in healthy controls and patients with infertility. Figure 1 shows a representative ultrasound image of a hydrocele found in the tunica vaginalis of one CML-CP patient, with a 0.9-cm-wide dark area of effusion.

3.4 Imatinib Treatment did not Significantly Affect Hormone Levels in Male CML-CP Patients

We examined sex hormone levels in the sera of CML-CP patients receiving imatinib to investigate further the effects of imatinib treatment on male fertility. Serum hormone levels, including FSH, LH, E2, P, T, and PRL, were within normal ranges and not significantly different from those of healthy individuals and patients with male infertility (Table 3).

4 Discussion

Imatinib causes dramatic clinical responses in CML patients, making it the standard of care for first-line treatment [8, 9]. These patients have a greater desire to live lives that are as normal as those of healthy individuals. Suggestions from physicians regarding fertility, pregnancy, and family planning for CML patients are, therefore, increasingly important [10, 11]. Imatinib is not recommended for female CML patients during pregnancy because of the potential harm to the foetus [12]. In contrast, there are no special precautions for male CML patients receiving treatment with imatinib. The risks and benefits of imatinib therapy for male CML patients who desire to have children must be evaluated on an individual basis.

Some experimental and clinical studies evaluated the possible implications of imatinib on the male reproductive system and male fertility. However, the results of these studies are not consistent. Some studies reported that imatinib affected the male reproductive system and reduced sperm count and motility [13–15]. Exposure to imatinib in early life also impacts the function of the reproductive system and fertility in rodents [16, 17]. Imatinib treatment during the first week of the postnatal stage in male rats delayed formation of the germline stem cell pool and increased apoptosis in germ cells. In vitro, imatinib reduced the growth of cultured spermatogonial stem cell and the number of differentiated spermatogonia in the culture [18].

More than 200 clinical cases reported that pregnancies of female partners of male patients taking imatinib at standard and higher doses did not increase the risk of congenital

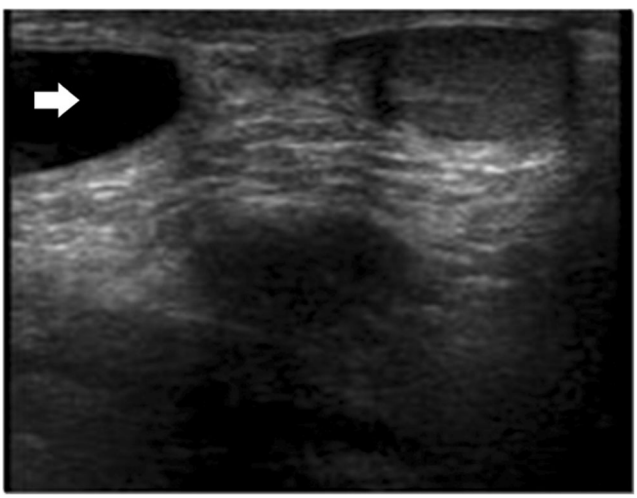

Fig. 1 Ultrasound image of the male reproductive system of a CML-CP patient. The arrow shows the hydrocele in the tunica vaginalis. The width of the dark area of effusion is 0.9 cm

Table 3 Sex hormone levels in serum

Items	CML-CP Group (n = 48)	Normal Control Group (n = 50)	Infertility Group (n = 10)
PRL(pg/mL)	224.18 ± 133.89	202.81 ± 96.99	181.72 ± 41.15
FSH(IU/L)	5.41 ± 2.53	6.44 ± 2.83	5.41 ± 1.57
LH(IU/L)	6.41 ± 1.35	7.27 ± 2.17	6.94 ± 2.88
T(μg/L)	10.9 ± 2.79	10.26 ± 2.65	9.61 ± 3.56
E2(μg/L)	34.18 ± 10.41	35.92 ± 13.81	33.83 ± 7.73
P(μg/L)	2.41 ± 0.99	2.75 ± 1.48	2.55 ± 1.13

The data are shown as the mean ± SD

abnormalities or spontaneous abortions [19]. Nicolini [20] recently reported sperm alterations in CML patients at diagnosis before any treatment. The authors suggested that these alterations were associated with the infiltration of granulocytic cells. They also measured sperm parameters in patients after a median of 16 (10–65) months of imatinib treatment and found that sperm alterations were not restored by imatinib treatment. In our study, semen samples from 48 CML-CP patients receiving imatinib treatment revealed lower sperm counts, reduced sperm survival rates, and reduced sperm activity in CML-CP patients compared with healthy individuals.

Oedema is a common adverse event during imatinib treatment owing to sodium retention. Testicular hydrocele was reported in patients with gastrointestinal stromal tumours (GISTs) and in acute lymphoblastic leukaemia (ALL) patients treated with imatinib [21, 22]. Ultrasound examination results regarding the reproductive systems of CML-CP patients revealed that the shape and size of their testes were comparable to those of healthy males. However, 19 of the 48 CML-CP patients were diagnosed with hydrocele in their tunica vaginalis, with enlargement in the size of the dark area of effusion, possibly due to sodium retention via the inhibition of c-KIT and PDGF.

The mean concentration of imatinib in the plasma of 48 CML-CP patients after imatinib treatment was 1524.14 ± 461.52 ng/mL, and all of these patients achieved complete remission after 3 months of imatinib treatment. This result is consistent with the pharmacokinetics/pharmacodynamics (PK/PD) analyses of the IRIS study, in which plasma imatinib levels greater than 1000 ng/mL correlated with improved cytogenetic and molecular responses [3]. Imatinib levels were similar in the plasma and semen (1471.18 ± 569.65 and 1397.27 ± 424.83 ng/mL, respectively), which indicated that imatinib penetrated the blood-testis barrier and may contribute to the reduced sperm count and activity in CML-CP patients.

Levels of FSH, LH, E2, P, T, and PRL in sera were normal in male CML-CP patients treated with imatinib. These results are consistent with previous clinical investigations. One prospective study of male CML patients demonstrated that imatinib barely altered FSH, LH, and E2 levels, while T fluctuated slightly during imatinib treatment. Similarly, this study also revealed reduced sperm counts in one of the two patients who underwent repeated examinations prior to and after imatinib treatment. The sperm count of the other patient declined at the beginning of imatinib treatment and recovered to normal levels after 6 months of imatinib treatment [23].

One previous case report from our hospital confirmed the present finding of the negative effects of imatinib on sperm parameters in CML-CP patients. A male CML-CP patient who had received imatinib treatment for 4 years, did not discontinue imatinib treatment at the time of conception. This patient exhibited a lower sperm survival rate (43.54%), and reduced sperm activity (16.7%). However, he successfully conceived, and a healthy baby was born after a normal pregnancy [24]. Follow-up on the baby was performed 36 months after birth, and the results demonstrated that the baby grew normally and remained healthy. Similar instances of the ability of male CML patients to conceive during imatinib treatment were reported, despite declines in sperm count, survival rate, and activity [25, 26]. However, more clinical studies are needed to evaluate the effects of imatinib on conception and fertility in male CMP patients.

In summary, this investigation suggests that imatinib crosses the blood-testis barrier and reduces sperm count, survival rates, and activity in CML-CP patients. However, reproductive organ structure and sex hormone levels were not affected. Future studies should elucidate the mechanisms of imatinib penetration of the blood-testis barrier and its effects on conception and fertility.

Compliance with Ethical Standards

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Conflict of Interest The authors declare no conflicts of interest.

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