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ORIGINAL ARTICLE

Effect of tyrosine kinase inhibitors on male fertility in patients with chronic phase chronic myeloid leukemia

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ABSTRACT

Advancements in the management of patients with chronic myeloid leukemia (CML) allowed them to achieve survival comparable with their healthy counterparts. Consequently, their care has widened with growing focus on quality of life, including parenting children. Although tyrosine kinase inhibitors (TKI) are contraindicated in pregnancy given their teratogenic effect, their effect on male fertility is less clear with contradictory results from animal studies and case reports/series. We compared the sperm analysis parameters, as the gold-standard assessment for male fertility, of 11 patients with CP- CML before and after TKI therapy. Median therapy duration was 5.1 years (range: 2.5–16.5). The sperm concentration, % progressive, and total motility before and after therapy were not significantly different ($p = 0.376$, 0.569, and 0.595, respectively). Our results suggest no impairment in fertility potential in male patients after TKI therapy. A larger sample size is crucial to support/refute our findings.

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Introduction

With the dramatic change in the prognosis of patients with chronic myeloid leukemia (CML) that was consequent on the introduction of tyrosine kinase inhibitors (TKIs) into clinical practice, the focus for patients and physicians has switched from prolonging survival to optimizing quality of life while on a life-long medication. One common concern is the effects of treatment on fertility and pregnancy outcomes. While the teratogenic effect of TKIs is well established, data on their effect on fertility, and especially male fertility, are scarce.

Evaluating male fertility in preclinical studies encompass the histological assessment of the gonads and glands involved in semen production, as well as semen analysis. In humans, semen analysis parameters (sperm number, motility, and morphology) remain the gold standard for assessing male fertility [1]. Whereas the majority of preclinical studies involving male animals reported adverse effects of TKIs on spermatogenesis, size and functions of the seminal vesicles, epididymis, testis, and prostate, as well as reduction in the number of pregnancies [2], reports in humans showed contradictory effects on spermatogenesis. Nevertheless, pregnancy outcomes in males exposed to TKIs were comparable to the normal population and indeed the recent management guidelines give no specific recommendations for men with CML to avoid TKI therapy before/at time of conception [3,4].

To investigate the effects of TKIs, if any, on spermatogenesis, we compared semen analysis parameters before and after TKI therapy in chronic phase (CP) CML patients treated in our institution.

Methodology

Patient selection/identification

In collaboration with the andrology department, we continue to offer sperm banking to men with newly diagnosed CML. Sperm analysis is undertaken as part of the process to ensure the quality of the banked samples.

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Patients followed up by the Imperial College Healthcare NHS Trust (ICHNT) hematology department who had sperm banking at diagnosis were identified through our departmental database. Patients with CP-CML who had cryopreserved semen at diagnosis and subsequently received TKIs were offered repeat semen analysis as standard of care. All patients consented to the general use of their data for research and publication (IRAS 288895).

Data collection

Demographic data, semen analysis results, and treatment history were collected from the electronic medical records. Semen analysis included sperm concentration ($\times 10^6$/ml), motility (% progressive and total), and morphology (% normal forms) when available. Data pertaining to pregnancy outcomes were also collected.

Semen analysis

Diagnostic semen analysis was conducted according to WHO 2010 guidelines (5th Edition) at a single laboratory with UKAS accreditation and UK NEQAS external quality control [6]. All semen analyses were performed before cryopreservation.

Statistical analysis

Median and range were used to summarize continuous nonparametric data. Paired sample *t*-test was used to compare continuous semen analysis parameters before and after TKI therapy. Double-sided p value of < 0.05 was considered as statistically significant. SPSS software (version 25, IBM, USA) was used for statistical analysis.

Results

Twenty-six patients diagnosed between 2001 and 2020 had semen analysis performed at the time of starting TKIs and were approached for repeat testing. Of those, 13 declined to participate, one lived overseas and was unavailable and one had stopped TKI therapy. Therefore, 11 patients were included in the analysis.

The median age at diagnosis was 34.4 years (range: 22.9–45.4). Seven and two patients received hydroxycarbamide (HU) and interferon (IFN), respectively, before TKI therapy but not before sperm collection. Table 1 summarizes therapies for the included patients. Six patients required 1 line of therapy only (imatinib, $n=4$; nilotinib, $n=1$; bosutinib, $n=1$), 3patients required 2 lines (imatinib followed by nilotinib; dasatinib followed by imatinib), and 2 required 3 lines (imatinib, dasatinib, nilotinib and imatinib, nilotinib, dasatinib).

The median duration of TKI therapy at the time of repeat semen analysis was 5.1 years (range: 2.5–16.5). Nine patients had sperm banking at diagnosis, but two (patients 6 and 10) had the initial semen analysis 736 and 475 days, respectively, from the start of their TKI therapy. All patients had a deep molecular response (at least MR4) at the time of the repeat semen analysis.

Table 2 summarizes the results of the initial and repeat semen analyses. In two patients (3 and 7), the semen parameters were below the reference ranges [6] on both occasions; no further investigations were initiated, but of note, the partner of patient 3 is expecting their first child shortly. Morphology (% normal forms) was less than the reference 4% in the repeat samples of five patients. The differences in sperm concentration, % progressive motility, and % total motility between initial and repeat semen analyses were all nonstatistically significant ($p=0.376$, 0.569, and 0.595, respectively).

Table 1. Demographics and therapies for included patients.

Patient ID	Age at diagnosis (years)	Received HU	Received IFN	TKI 1	Duration on TKI 1 (days)	TKI 2	Duration on TKI 2 (days)	Reason for switch**	TKI 3	Duration on TKI 3 (days)	Reason for switch**	Total duration on TKI (days)*
1	39	Y	Y	IM	6037	NA			NA			6037
2	37	N	N	BOS	1386	NA			NA			1386
3	23	N	N	IM	705	NIL	490	Failure	NA			1195
4	45	Y	N	IM	5707	NA			NA			5707
5	27	N	N	IM	1872	NA			NA			1872
6	37	Y	N	IM	251	DAS	31	Failure	NIL	2546	Intolerance	2825
7	37	N	N	IM	1350	NA			NA			1350
8	31	Y	Y	IM	944	NIL	926	Intolerance	NA			1870
9	32	Y	N	NIL	3560	NA			NA			3560
10	34	Y	N	IM	182	NIL	373	Failure	DAS	1910	Failure	2465
11	29	Y	N	DAS	818	IM	110	Intolerance	NA			928

BOS: bosutinib; DAS: dasatinib; HU: hydroxycarbamide; IM: imatinib; IFN: interferon; N: no; NA: not applicable; NIL: nilotinib; Y: yes.
*Calculated as the time between the start of TKI therapy and the date of the repeat semen analysis (post TKI).
**Based on the ELN criteria [5].

Table 2. Initial and repeat semen analyses.

	Initial/pre-TKI sample			Repeat/post-TKI sample				Time between samples (days)
Patient ID	Sperm/ml (x10^6)	% Progressive motility	% Total motility	Sperm/ml (x10^6)	Morphology (% normal forms)	% Progressive motility	% Total motility	
1	16	44	54	4.2	2	NA	NA	6113
2	166	94	97	182.8	5	64	71	1413
3	5	15	17	3.2	NA	26	32	1209
4	167	45	55	277.5	5	54	58	5785
5	32	46	50	19.5	3	63	71	1892
6	118	61	68	208.5	2	52	56	2093
7	10.4	12	16	12.1	2	28	37	1361
8	20.4	67	71	27.6	1	45	53	1891
9	145	58	73	48.1	10	48	55	3567
10	185.8	80	87	223.5	4	64	68	2023
11	17.7	34	45	44.6	4	37	47	936

NA: not available.
Morphology was not available for any of the initial samples.
Reference ranges (≥ 15 × 10^6 sperm/ml; ≥ 32% progressive motility; ≥ 40% total motility; ≥ 4% normal forms) [6].
Values in red are below the reference range.

Two patients successfully conceived while on TKI therapy (including patient 3 despite of sub-normal semen analysis parameters pre- and posttherapy)and the remaining 9 did not attempt to conceive after diagnosis (Supplementary TABLE 1).

Discussion

Testicular development and spermatogenesis are dependenton the expression of the tyrosine kinases, c-KIT and PDGFR-α, and Leydig cells are known to express PDGFR [2,7] and are therefore prone to the off-target side effects of TKIs designed to inhibit *BCR::ABL1*. Furthermore, tyrosine kinases are crucial for capacitation, the process by which sperms gain fertilizing capacity during their passage through the female genital tract, and the acrosome reaction [8].

Animal studies of the available TKIs, performed to obtain market authorization, showed different effects for each TKI on male fertility. Imatinib resulted in a reduction in the size of the testes and epididymis, and sperm motility [9], bosutinib caused a reduction in the number of pregnancies in mated females [10], dasatinib was associated with reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis [11], ponatinib caused degeneration of testicular epithelium [12], whereas nilotinib [13] had no effect on fertility or spermatogenesis. However, further animal studies after licensing were not clear-cut, but showed contradictory results. For imatinib, Schultheis et al. [14] showed no difference in the morphological appearance of the mice testes between treatment and control groups. On the other hand, Heim et al. [15] showed a reduction in the number of differentiated spermatogonia, Hashemnia et al. [16] found significant decrease in mouse TM4 Sertoli cell viability, and Ahmadi et al. [17] showed a decrease in sperm density and motility in Zebra fish after imatinib administration. For nilotinib, Seval et al. [18,19] showed no changes in spermatogenesis in mice after administration of nilotinib, whereas Ozkavukcu et al. [20] showed both lower pregnancy rates and testicular histological scores in male mice that received nilotinib, and Khaleel et al. [21] showed adverse histological changes in the seminiferous tubules and reduction in spermatogenesis in mice receiving nilotinib as compared to controls. No data are available for dasatinib, bosutinib, or ponatinib. Attempts to extrapolate these results to the clinical setting are confounded by the lack of information regarding the TKI plasma concentrations achieved in the various animal models.

For patients with CML, the majority of the available data focus on pregnancy outcomes following maternal, rather than paternal, exposure to TKIs (reviewed by Palani et al. [22], Abruzzese et al. [23], and Rambhatla et al. [24]. Carlier et al. reported 15 cases of paternal exposure to TKI at conception from the French pharmacovigilance network and summarized similar published cases. As most of the pregnancies in their series were carried to term, it was not possible to conclude a causal relation between paternal exposure to TKI at conception and the small number of adverse outcomes noted (1 early spontaneous abortion and 3 children with anomalies, including complex cardiac malformation requiring surgical correction, pyeloureteric junction syndrome managed conservatively, and mild pulmonary valve stenosis managed conservatively. The latter also developed acute myeloid leukemia at 19 months of age) [25]. In their systematic review of pregnancy outcomes for fathers receiving TKIs at conception, Szakács et al. concluded that 93.5% of the pregnancies (400/428 pregnancies for 374 men) ended in a live birth. The rate of congenital malformations, quoted at 3.5%, was not different from that reported in the

general population [26]. Similarly, several case reports and case series reported successful pregnancies for fathers treated with imatinib at conception [27–30]. Cortes et al. reported on the outcomes of 17 cases of paternal exposure to bosutinib identified from the Pfizer safety database. Nearly half of the pregnancies ended with healthy live births ($n=9$), four had induced abortions and 1 had a spontaneous abortion, none of which were considered to be related to bosutinib, and in 3 the outcome was not known at the time of publication [31]. For ponatinib, of the 22 partner pregnancies, 10 resulted in healthy deliveries, nine had unknown outcomes and three resulted in miscarriages (personal communication with Incyte).

In contrast to the above encouraging outcomes, Chang et al. showed the deleterious effects of imatinib on spermatogenesis, in terms of sperm count, activity, and survival [32]. Oligospermia was found in 2 patients treated with imatinib (one was treated for hypereosinophilic syndrome [33], rather than CML, and in the other patient imatinib was started before puberty) [34]. Yassin et al. found similar effects on semen parameters (count, motility, and morphology) in 20 patients with CML after treatment with imatinib, nilotinib and dasatinib for 4 months. The effects of dasatinib were less pronounced than those of imatinib and nilotinib [35]. A major limitation of the latter study is the small sample size and the lack of information about the number of patients receiving each TKI. Nicolini et al. [36] reported low numbers of spermatozoa/ml in eight patients with CML after a median of 16 months of imatinib treatment.

In our patient cohort, no significant differences were found in sperm concentration or motility before and after treatment with different TKIs, at varying doses, for a prolonged period. These findings contrast the findings from the above-mentioned studies.

Two patients successfully conceived after diagnosis without interrupting TKI therapy. The remaining 9 patients did not attempt to conceive after diagnosis. The small number of patients with a favorable pregnancy outcome makes drawing further conclusions not possible.

The relevance of the finding of a low percentage of normal forms, in the presence of normal sperm concentration and motility, in some of the patients in the semen sample after TKI therapy is not clear, especially in the absence of pretreatment values for comparison. However, this might be similar to the higher percentage of abnormal sperms in CML patients, when compared to the healthy population, reported by Nicolini et al. [36]. A larger sample size with pre- and post-treatment samples would be needed to confirm or refute this finding.

Limitations of our study include the small sample size and the lack of data on morphology of the pre-TKI semen samples. Incorporating pregnancy outcomes for both males and females treated with TKI at conception in a population-based CML registry would allow the collection of a large enough sample size to allow the provision of evidence-based decisions to the CML patients in relation to their fertility.

In conclusion, our study did not show statistically significant effect of TKI treatment on the semen analysis parameters inpatients with CP-CML. Although the sample size of our cohort was small, to the best of our knowledge, it is the largest cohort with paired samples.

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Authorship statement

GN: collected and analyzed the data, wrote the manuscript.

SC, DM, IC, JC, JFA, AI, PM, FF: critically appraised the manuscript.

RS: advised on statistical analyses.

SL: helped with data collection.

Disclosure statement

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