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Gonadal Function in Male Patients With Metastatic Renal Cell Cancer Treated With Sunitinib

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Abstract. *Background/Aim: Single-agent tyrosine kinase inhibitors are still prescribed as first-line treatment to a relevant subgroup of patients with metastatic renal cell carcinoma (mRCC). These agents are known to cause disfunction of many endocrine glands (e.g., thyroid). In this two-step trial, we aimed to assess gonadal function among male patients with mRCC treated with sunitinib. Patients and Methods: We enrolled a first cross-sectional cohort of pre-treated (>6 months) patients and a subsequent cohort of treatment-naïve patients who were prospectively followed-up. All patients were screened for hypogonadism and received a Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire at study entry and after 6 months of therapy. Patients who were candidates for testosterone replacement therapy (TRT) also received a FACT-G questionnaire at baseline and 3 months after supplementation. Results: Among the 30 enrolled patients, the prevalence of hypogonadism was found to be higher in those receiving sunitinib for a longer period (27.3% at baseline, 41.7% in the first 6 months, and 68.4% after 9 months of therapy). The testosterone level of patients correlated with quality of life (R=0.32). A total of six patients received TRT, with a significant improvement in their global quality of life after the first 3 months of treatment. Conclusion: An increasing prevalence of hypogonadism was seen among male patients who received long-term treatment with sunitinib. TRT was associated with relevant improvements in quality of life. These findings corroborate similar published observations and encourage the assessment of gonadal function in male patients with mRCC under treatment with sunitinib.*

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Sunitinib malate is an orally, multitargeted tyrosine kinase inhibitor currently approved for the treatment of metastatic renal cell carcinoma (mRCC), imatinib-intolerant or refractory gastrointestinal stromal tumors and advanced well-differentiated pancreatic neuroendocrine tumors (1, 2). The sunitinib kinome spans across multiple targets, including kinases involved in angiogenesis such as vascular endothelial growth factor receptors 1-3, platelet-derived growth factor receptors α and β, stem cell growth factor, FMS-like tyrosine kinase 3, colony-stimulating factor 1 receptor, and glial cell line-derived neurotrophic factor receptor (3). Most of these kinases are also involved in the metabolic pathways of healthy tissues, thus explaining the heterogeneous side-effects of sunitinib. In addition to those strictly related to angiogenesis (*i.e.*, hypertension or cardiac toxicity), sunitinib typically induces organ-specific (*i.e.*, diarrhea, hand–foot syndrome, stomatitis, thrombocytopenia, or neutropenia) and general toxicities (*i.e.*, fatigue and asthenia).

Regarding fatigue, its incidence in phase 3 studies ranged between 14% and 51% for toxicities of all grades, and up to 11% for grade 3-4 events (4, 5), being one of the most prevalent reasons for schedule modification, dose reduction or therapy discontinuation. Although its multitargeted profile makes it difficult to identify a unique biological substrate for sunitinib-induced fatigue, the high incidence of hypothyroidism is often proposed as its basis (6). Besides hypothyroidism, derangements in other endocrine glands among patients treated with sunitinib have been investigated and reported in the

literature (7-9). Of note, the prevalence of hypogonadism was found to increase significantly throughout treatment and to be correlated with fatigue (10-12). Testosterone replacement therapy (TRT) was demonstrated to lead to a clinically relevant improvement in quality of life (QoL) among patients with hypogonadism and fatigue in a randomized clinical trial (12). We aimed to further investigate the prevalence of hypogonadism in male patients receiving sunitinib as first-line treatment for mRCC, at different timepoints.

Patients and Methods

This single-center study was conducted at the Medical Oncology Unit of Azienda Socio Sanitaria degli Spedali Civili in Brescia (Italy). The study concept included two phases. The first cross-sectional phase was designed to include male patients with mRCC receiving first-line sunitinib for at least 6 months. In the second prospective phase, we enrolled consecutive patients with mRCC who were prospectively evaluated at baseline and during sunitinib administration (at 6 weeks, 6 months and at 6-9 months from the beginning of therapy).

All patients from both groups provided fasting serum and plasma samples (between 8 am and 10 am) for the assessment of male gonadal function and subsequently underwent an endocrinological assessment. Hormonal assays were performed at our University Hospital at the same laboratory. The male gonadal hormonal evaluation included serum levels of luteinizing hormone (LH), sex hormone-binding globulin, total testosterone (TT) and calculated free testosterone (cFT). LH and TT were evaluated by a commercial electrochemiluminescence immunoassay method, while cFT was calculated based on sex hormone-binding globulin concentration according to the Vermeulen formula (13). Male hypogonadism was defined according to current clinical guidelines (14-17) as follows: Primary hypogonadism: LH >9.4 IU/I, TT <3.5 ng/ml and cFT <63 pg/ml; secondary hypogonadism: LH <1.5 IU/I, TT <3.5 ng/ml and cFT <63 pg/ml; normogonadotropic hypogonadism: 1.5<LH<9.4, TT <3.5 ng/ml and cFT <63 pg/ml; or subclinical hypogonadism: LH >9.4 IU/I, TT ≥3.5 ng/ml and cFT ≥63 pg/ml.

TRT was proposed to men with overt hypogonadism in addition to symptoms such as reduced libido, erectile dysfunction, decreased morning erections, fatigue and muscle weakness, after the exclusion of specific contraindications (*i.e.*, uncontrolled heart failure, recent major acute cardiovascular event, prostate-specific antigen >4 ng/ml, untreated prostate or breast cancer, severe low urinary tract symptoms, hematocrit >48-50%) (15, 17).

The Functional Assessment of Cancer Therapy General (FACT-G) questionnaire (18) for QoL evaluation was administered to all patients at study entry, after 6 months of treatment with sunitinib (in the prospective cohort) and, in patients submitted to TRT, after 3 months of therapy.

Standard first-line treatment consisted of 50 mg sunitinib daily, according to a classic 6-week schedule (4 weeks on and 2 weeks off therapy). Schedule modification and dose reductions were allowed as per common clinical practice. Patients had no food or medical restrictions, and medications other than sunitinib were not standardized. All patients provided their informed written consent before the beginning of the study.

The primary endpoint of the study was to define the prevalence of hypogonadism in the overall population of sunitinib-treated patients. As secondary endpoints, we analyzed the prevalence of hypogonadism among sunitinib-naive patients, the classification of hypogonadism among subtypes, the correlation between serum testosterone levels and QoL, and changes in QoL upon beginning of TRT.

Table I. *Patient characteristics*.

Characteristic	Cross-sectional cohort	Prospective cohort
Male, n	17	13
Median age (years)	61.6	62.4
Nephrectomy, n	16	8
Site of metastases, n		
Lung	11	8
Lymph nodes	9	4
Liver	4	3
Adrenal glands	4	0
Kidney	4	2
Bone	3	2
Brain	0	2
Pancreas	1	0
Pleura	0	3

Results

Prevalence of hypogonadism at baseline. Overall, 30 men were enrolled and provided serum samples, divided between the cross-sectional phase (N=17) and the prospective phase (N=13). Patients' characteristics are summarized in Table I. The prevalence of hypogonadism in the overall population is reported in Figure 1.

Among the 13 men prospectively followed-up, only 11 provided baseline gonadal assessment. At baseline (before the beginning of sunitinib), the prevalence of hypogonadism was 27.3% (three out of 11), and was entirely normogonadotropic.

Prevalence of hypogonadism during sunitinib treatment. Among 13 men from the prospective cohort, 12 underwent gonadal function assessment between 6 weeks and 6 months after beginning sunitinib: Hypogonadism was found in five patients (41.7%), of whom four (80%) were normogonadotropic and one (20%) was subclinical. Seven men from the same cohort received hormonal evaluation between 6 and 9 months after the beginning of treatment: hypogonadism was evident in three (42.9%), of whom two were normogonadotropic and one was subclinical. Finally, 19 men from both the cross-sectional and prospective cohorts underwent gonadal function assessment after 9 months or more from beginning sunitinib; 13 of them (68.4%) showed hypogonadism: two had primary hypogonadism, one secondary, seven (53.8%) were normogonadotropic and three were subclinical.

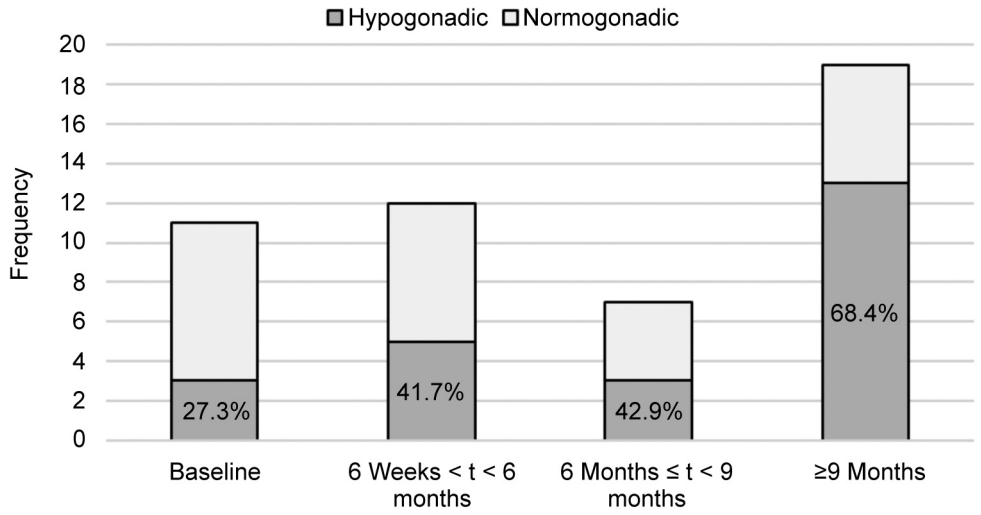

Figure 1. *Prevalence of male hypogonadism in the overall population.*

Quality of life and TRT. The QoL score as assessed through FACT-G questionnaire significantly deteriorated during the treatment period when compared to baseline (median global score of 64 points *versus* 79, respectively) (Figure 2), exceeding the 5-point threshold of clinical significance for the FACT-G scoring system (19). Regarding specific items, none of the four subscales (namely physical, social, emotional, and functional) significantly worsened after the beginning of the therapy. When comparing hormonal levels with QoL scores, only cFT showed a slight correlation with physical comfort (Pearson R=0.32, Figure 3).

Overall, six patients received TRT after the diagnosis of clinically relevant hypogonadism.

TRT was started at about 6 months after beginning sunitinib in two men, while after more than 9 months in the other four patients. Testosterone enanthate at 125 mg/month and 2% testosterone gel at 20 mg/day were administered to four and two hypogonadal men, respectively.

Among patients assigned to hormonal replacement, a significant benefit in QoL was observed after 3 months of TRT and there was normalization of the TT level, with a median improvement of 11.5 points in FACT-G global score (Figure 4), which is far above the upper boundary of clinical relevance. Of note, the items which benefited most were not limited to physical and functional wellbeing, but also extended to the social area. Changes in QoL per single item among patients receiving TRT are shown in Figure 5.

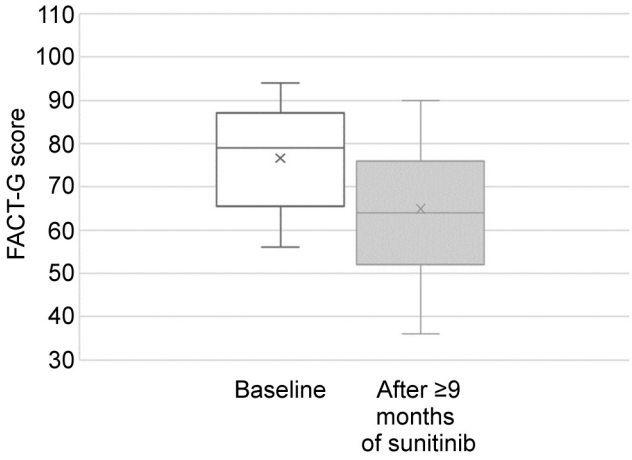

Figure 2. *Quality of life assessed through Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire at baseline and after at least 9 months of sunitinib treatment. ×: Mean value; line: median value; box: 25-75% percentiles; whiskers: minimum-maximum values.*

Discussion

After the publication of recent phase III trials showing survival benefit in favor of immunotherapy-based combination therapies (20-23), sunitinib is no longer the standard of care for first-line therapy in mRCC. However, there may still be a subgroup of patients who will be treated with sunitinib upfront (*e.g.*, good-risk patients and those unfit for combination therapies) and in subsequent lines. It is known from randomized trials, as well as real-world data, that patients receiving sunitinib encounter chronic adverse events, resulting in QoL deterioration (24). Fatigue is among the most reported side-effects (14-51% for all-grade toxicity, up to 11% for grade 3-4) (4, 5). Although hypothyroidism has long been proposed as a contributing factor to sunitinib-induced fatigue, recently some evidence was published reporting the incidence of hypogonadism (9-12) and the

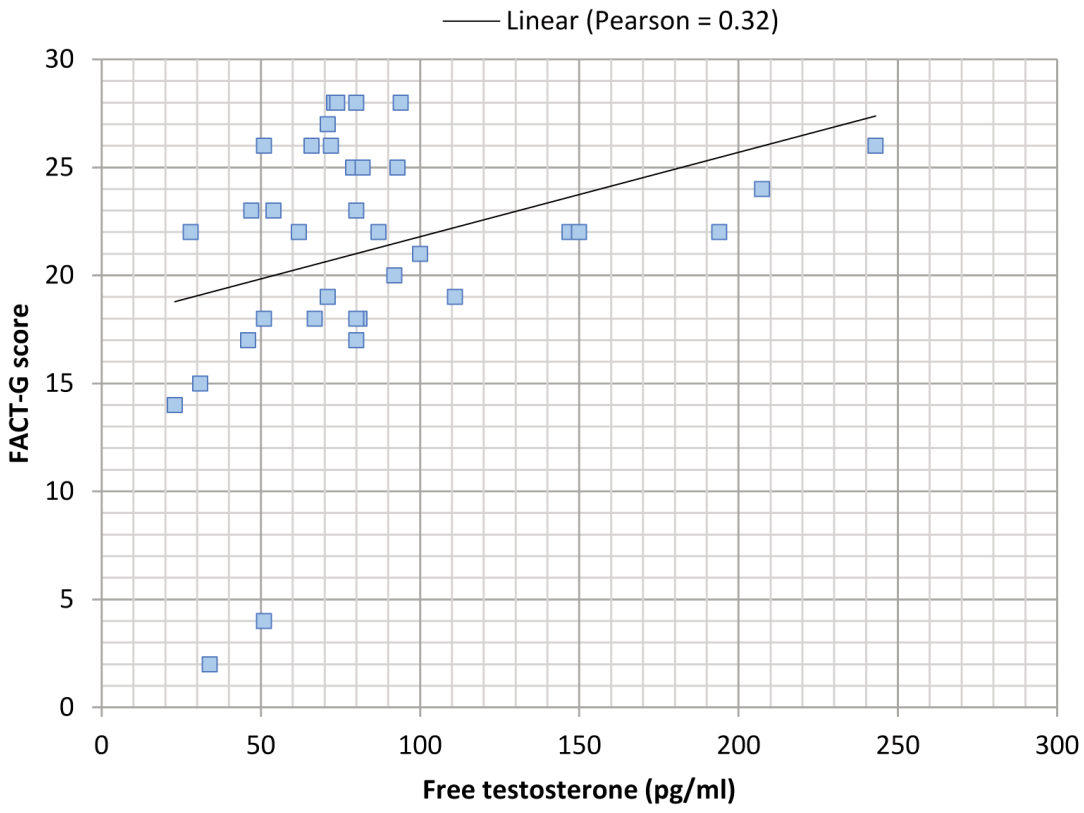

Figure 3. *Correlation between calculated free testosterone and physical well-being.*

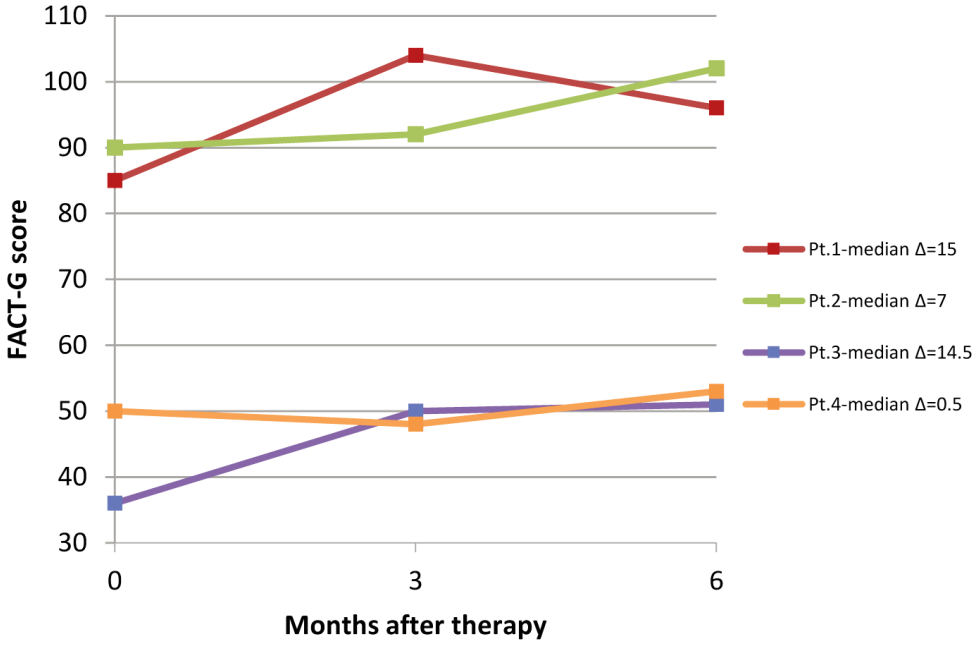

Figure 4. *Overall benefit in quality of life by Functional Assessment of Cancer Therapy – General (FACT-G) score among patients after testosterone replacement therapy. Δ: Change in value.*

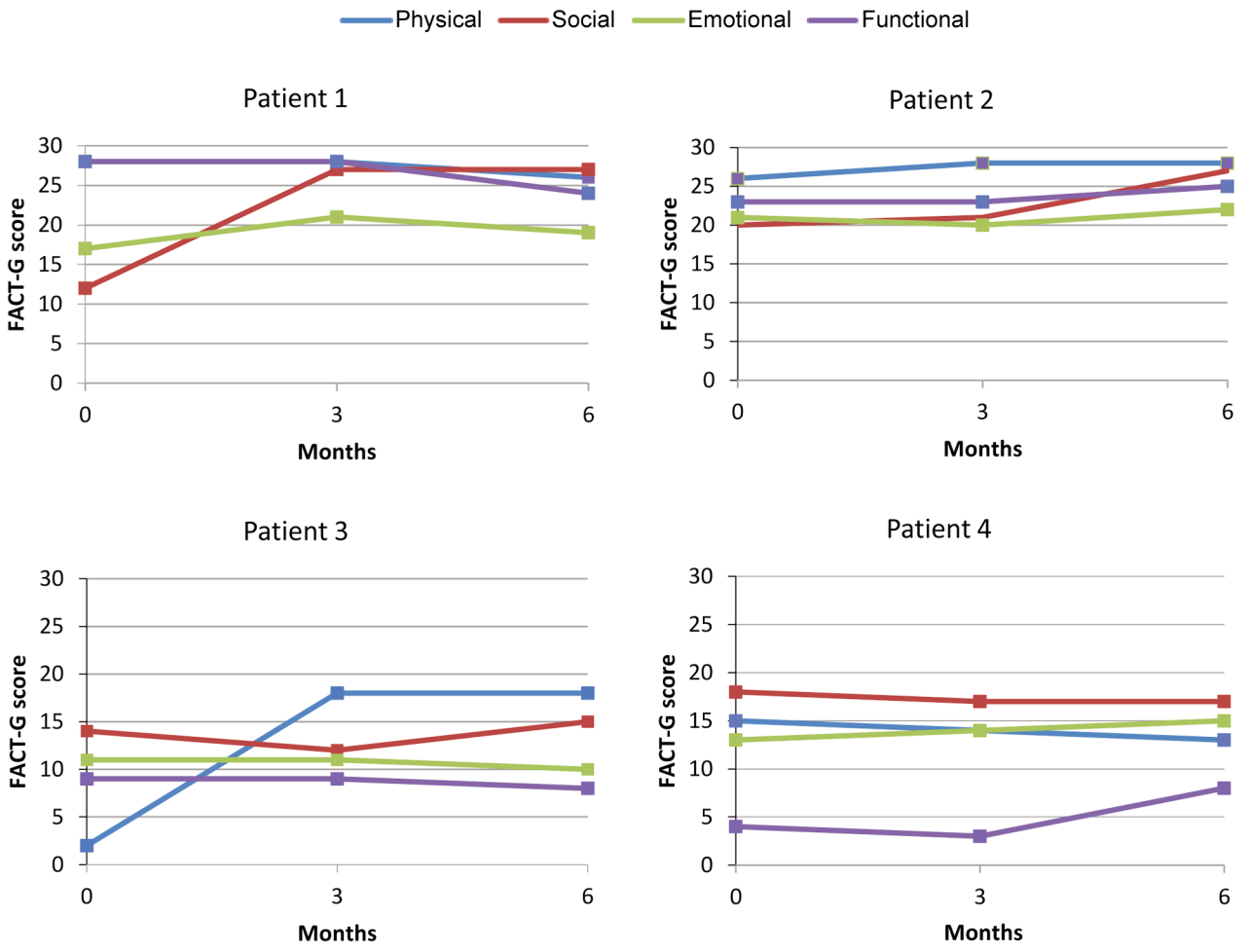

Figure 5. *Functional Assessment of Cancer Therapy – General (FACT-G) score by domain among patients after testosterone replacement therapy.*

effects of testosterone replacement on fatigue (12) among two series of patients with mRCC treated with sunitinib.

In our analysis, we showed a relevant prevalence of hypogonadism especially among patients receiving sunitinib for more than 9 months (68.4%), although it was a common finding even in sunitinib-naive patients and in the first 9 months. The most represented subtype was normogonadotropic hypogonadism (inappropriately normal LH despite testosterone decline), suggesting that sunitinib might have an inhibitory effect on gonadal function at both the testicular and pituitary level.

We also showed that men with clinically relevant hypogonadism do benefit from TRT in terms of a global QoL improvement as early as after 3 months of therapy.

These findings are in line with previous report of a high incidence of hypogonadism among men receiving sunitinib (9-12), suggesting that gonadal function should be assessed at baseline and throughout treatment. Furthermore, our results favor a moderate correlation between testosterone levels and QoL (*i.e.*, physical comfort area) being reinforced by the observation of a clinically significant QoL benefit in those patients receiving TRT.

This study suffers from several limitations, such as the small population, which enabled us to produce only descriptive statistics, the absence of a fully prospective design, and the lack of standardization for possible confounding factors (*i.e.*, food and concomitant medications).

However, the study design allowed us to analyze the prevalence of hypogonadism during the treatment period, showing an increasing prevalence in patients with a long-term exposure to sunitinib (in approximately two out of three cases after 9 months of therapy). Of note, the majority of patients who were candidates for TRT were receiving sunitinib for more than 9 months.

In conclusion, during treatment with sunitinib, a significant proportion of male patients can develop clinically

relevant hypogonadism, partially explaining the high incidence of treatment-induced QoL deterioration. Men with overt hypogonadism and without specific contraindications can receive TRT to gain a meaningful improvement of clinical symptoms. We suggest that gonadal function should be assessed as part of routine laboratory evaluation in patients submitted to sunitinib for mRCC.

Conflicts of Interest

The Authors declare that there are no conflicts of interest.

Authors' Contributions

A.D.V.: Conceptualization, article writing. A.D., C.C. and A.F.: Article writing, I.C., M.B. and F.V.: Article editing. A.B.: Supervision conceptualization and article editing.

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