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Research Paper

Impact of adjuvant imatinib on bone and muscle density in patients with resected gastrointestinal stromal tumors

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ABSTRACT

Adjuvant treatment with Imatinib is the standard of care for high-risk resected GISTs. Imatinib is known to have an impact on bone mineral density in patients affected by chronic myeloid leukemia, however this effect has never been investigated in GISTs.

We retrospectively evaluated, on CT scans, the effect of adjuvant Imatinib (400 mg/die) on bone mineral density and muscle composition in 14 patients with surgically resected GISTs and in a control group of 8 patients who did not received any treatment. The effect of bone and muscle composition on Imatinib-tolerance was assessed as well.

Overall patients receiving Imatinib experienced an increase in bone mineral density during treatment ($p = 0.021$); with higher increase in patients with basal values < 120 mg/cm^3 ($p = 0.002$). No changes were observed in the control group ($p = 0.918$).

Skeletal muscle index and lean body mass did not change over time during Imatinib therapy; however, patients with lower lean body mass and lower body mass index experienced more grade 3 treatment related toxicities ($p = 0.024$ and $p = 0.014$ respectively). We also found a non-significant trend between basal BMD and grade 3 toxicities ($p = 0.060$)

1. Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors with an estimated incidence of 10–15 cases per million every year [1]. The treatment for non-metastatic GISTs is surgical resection. Three years of adjuvant treatment with Imatinib (400 mg/die) is recommended for tumors with high-risk features and c-KIT mutations [2].

Imatinib is an orally available tyrosine kinase inhibitor (TKI) that targets c-abl, c-KIT and PDGFR; at therapeutic concentration it can also inhibit the macrophage-colony stimulating factor (M−CSF) receptor [3]. Imatinib is currently approved for the treatment of chronic myeloid leukemia (CML) and GISTs in adjuvant, neoadjuvant and metastatic settings [4]. There is evidence that Imatinib can influence bone metabolism [5]. In *in vitro* and *in vivo* murine models, Imatinib can promote osteoclasts apoptosis and can inhibit their differentiation [6], contextually stimulating osteoblast differentiation [5] mainly through PDGFR inhibition.

In CML patients, Imatinib treatment has been associated to alterations in serum markers of bone metabolism [7] as well as to radiological and histological evidences of increased trabecular bone volume and thickness [8]. The effect of Imatinib on bone composition in patients receiving treatment for GISTs has not been investigated. There is a weak evidence that Imatinib, in patients affected by GISTs, can have a role in influencing muscle composition [9], which is closely related to bone health [10].

Bone and muscle composition have recently been correlated with drug-related toxicities [11], quality of life, performance status and prognosis in patients affected by solid cancer [12]. The prevention, diagnosis and treatment of alterations in these tissues are of particular interest in patients with long life expectance, as those receiving adjuvant treatment. Here, we hypothesized that Imatinib treatment could have an effect on bone mineral density (BMD) and muscle composition. We also assessed the role of these anthropometric parameters on Imatinib-related toxicities.

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2. Materials and methods

2.1. Study design

We conducted a single center retrospective study to evaluate the effect of Imatinib on bone and muscle composition in patients with radically resected GIST at our institution (University Campus Bio-Medico of Rome) between October 2009 and June 2020. To avoid the effect of confounding factors we excluded patients with metastatic disease. The study was approved by the local ethics committee.

2.2. Patients

We retrospectively selected patients with surgically resected high-risk GIST that completed 3 years of adjuvant therapy with Imatinib (starting dose 400 mg/die). Imatinib was started within 30 days from baseline CT scan and within 60 days from surgery. Patients electronic charts were reviewed. Patients that progressed during treatment, those lost during follow-up or without a baseline CT scan (at least 30 days before starting Imatinib), and at least 3 subsequent CT scans at 6, 12 and 18 months, were excluded. To confirm the potential effect of Imatinib on bone density, we subsequently selected a control group from patients with low risk surgically resected GIST, who did not receive adjuvant treatment.

Age at diagnosis, sex, height, weight, date of surgery, prognostic features according to Joensuu's classification [13], Imatinib toxicities and dose reduction were recorded by two investigators in a predefined data form. For the age variable, patients were dichotomized based on the median value. Height and weight were recorded with standard procedures before starting Imatinib therapy. They were used to calculate BMI [weight (kg)/height $(m)^2$]. Toxicities were assessed at each visit by Common Terminology Criteria for Adverse Events (CTCAE) v.4. Grade 3 toxicities led to dose reduction and grade 4 to Imatinib discontinuation with consequent exclusion from the final analysis. Disease progression was defined per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.

2.3. Bone and muscle density evaluation

Muscle and bone density were evaluated on CT scan by two dedicated radiologists at baseline and after 6, 12 and 18 months. BMD was evaluated at third lumbar vertebra in axial slice. Hounsfield units (HU) density of the bone was calculated selecting a region of interest (ROI) in the anterior vertebral body, avoiding the cortex. A density $\geq$ 120 mg/cm^3 was considered normal, osteopenia was defined as a density between 80 and 120 mg/cm^3 and osteoporosis if density was < 80 mg/cm^3. Muscle density was assessed evaluating two consecutive images at 3 lumbar vertebra (L3) by a dedicated radiologist trough Oxiris software. Muscles were detected considering anatomical landmarks and specific Hounsfield values (from −29 to + 150) for skeletal muscles [14]. Data about the paraspinal, psoas and abdominal wall muscles were collected, cross-sectional areas (cm^2) of the sum of all these areas were calculated, and the mean value for two consecutive images was calculated. This value was then divided per height squared [15] to obtain the lumbar skeletal muscle index (SMI). Patients were defined sarcopenic if their SMI was < 39 cm^2/m^2 for women and < 55 cm^2/m^2 for men [16]. Total lean body mass (LBM) was extracted using Mourtzakis formula (LBM (kg)=(0.30 × (skeletal muscle area at L3 using (cm^2)) + 6.06) [17].

2.4. Statistical analysis

Patient characteristics at baseline were compared using Fisher's exact test for categorical variables and Mann-Whitney-Wilcoxon for continuous variables. Continues variables were reported as median and range. Correlations and simple linear regression analyses were calculated for the following pairs of continuous variables: baseline BMD and SMI, baseline BMD and LBM, baseline BMD and BMI, baseline LBM and BMI, baseline SMI and BMI, and baseline BMD and the difference between final and baseline BMD (delta BMD). Pearson's r and r^2 coefficients were reported. Changes of BMD over the different time points were analyzed using a one-way repeated measures analysis of variance by ranks (Friedman test). All reported p values were two-sided. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 8.2 (GraphPad Software, La Jolla CA, USA).

3. Results

3.1. Baseline characteristics

In total we screened 25 patients eligible for adjuvant Imatinib. After removing those who experienced disease progression or those lost at follow-up, 14 patients were eligible for the final analysis (6 women and 8 men) (Fig. 1). Considering this group of cases, the median age at diagnosis was 69.1 years (range: 35.9–82.5); all the women were post-menopausal. All the patients had GIST with high-risk features per Joensuu's classification. Five (35.7%) were of gastric origin. At baseline, prior to Imatinib therapy, the median BMI was 24.6 kg/m^2 (range: 17.8–30.1); the median BMD was 110.5 mg/cm^3 (range: 52–175); median SMI and LBM were 42.6 cm/m^2 (range: 30.8–56.1) and 41.3 kg (range: 26.8–58.1) respectively (Table 1).

Considering the parameters of the case group at baseline, 8 (57.1%) patients had a BMD below the normal limit (2 osteoporotic and 6 osteopenic) and 4 (28.6%) were sarcopenic. Men had a significantly higher BMD, SMI and LBM at baseline compared to women (median BMD: 142.5 vs 83.0: p = 0.013; median SMI: 45.0 vs 37.3; p = 0.018; median LBM: 46.5 vs 32.3: p = 0.001) (Fig. 2).

BMD was positive associated with SMI (p = 0.039, r = 0.556, r^2 = 0.309) and LBM (p = 0.005, r = 0.746, r^2 = 0.556) (Suppl. Fig. 1A and 1B). We also observed a significant association between BMI and SMI (p = 0.041, r = 0.550, r^2 = 0.303) as well as a non-significant association between BMI and LBM (p = 0.058, r = 0.517, r^2 = 0.267) (Suppl. Fig. 1C and 1D). BMD, SMI and LBM did not correlate with age and site of primary tumor in cases.

3.2. Impact of Imatinib on BMD

In our population, SMI and LBM did not significantly change during the first 18 months of Imatinib therapy (p = 0.787, p = 0.955 respectively). On the contrary, BMD showed an overall significant increase over time (p = 0.021) (Fig. 3A). A significant inverse correlation between baseline and delta BMD (difference between baseline and last record) was found (p = 0.021, r = -0.653, r^2 = 0.426) (Fig. 2B), with most patients with lower basal BMD reporting an increase in BMD during Imatinib therapy and conversely most patients with higher basal BMD reporting a stable or decreasing BMD.

Considering these data, we separately analyzed BMD changes in the 8 and 6 patients with BMD at baseline respectively < 120 mg/cm^3 and $\geq$ 120 mg/cm^3 (Table 2). In the subset of patients with lower BMD, it showed a significant increase over the different time points (6, 12, 18 months) (p = 0.002) (Fig. 3C), whereas there was no significant change over time in the remaining patients with higher BMD (p = 0.993) (Fig. 3D). Considering the above findings, we decided to select a control group made up by patients with low basal BMD, affected by low risk resected GIST who did not receive Imatinib therapy.

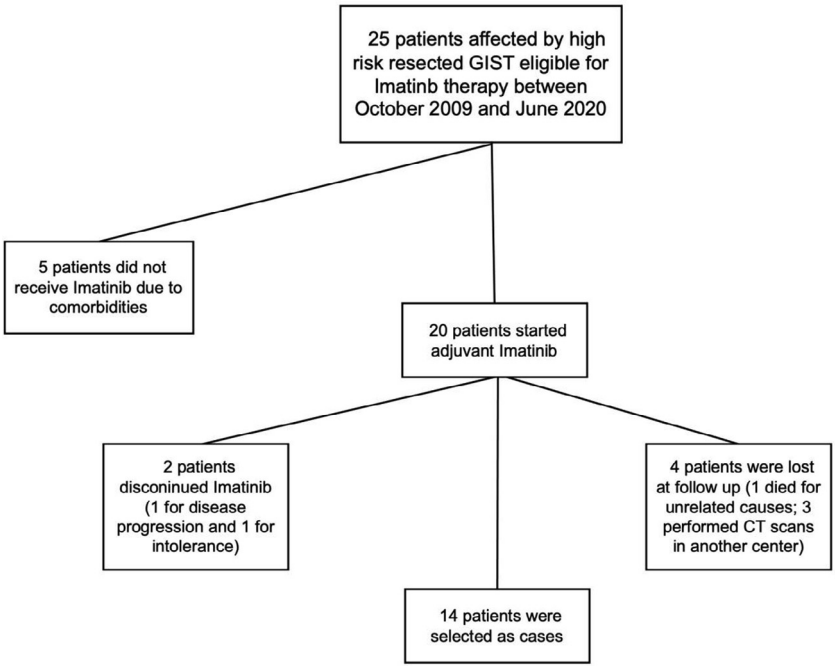

Fig. 1. Patients eligible for the final analysis.

Table 1
Basal characteristics of case group.

Number	14
Age (Median; Range)	69.1 years; 35.9–82.5
Gender: N (%)	6 women (42.9%) 8 men (57.1%)
Site of primary tumor: N (%)	6 small bowel (42.9%) 5 stomach (35.7%) 2 rectum (14.3%) 1 retroperitoneum (7.1%)
BMI Median; (Range)	24.6 kg/m^2; (17.8–30.1)
BMD Median; (Range)	110.5 mg/cm^3; (52–175)
LBM Median; (Range)	41.3 kg; (26.8–58.1)
SMI Median; (Range)	42.6 cm/m^2; (30.8–56.1)

In total, 8 patients (4 women and 4 men), with a median age of 70.4 years (range: 61.9–75.6) and a basal median BMD of 83.0 mg/cm^3 (range 59–119) constituted the control group. Controls were all affected by gastric low risk GIST and they did not significantly differ from cases in terms of baseline characteristics (age; gender; BMD, SMI, LBM and BMI) (Table 3). Also in this group all the women were post-menopausal. In this group, the BMD did not significantly change over the course of 18 months of follow-up (p = 0.918). Similarly, LBM (p = 0.522) and SMI (p = 0.583) remained stable over time (Suppl. Fig. 2).

3.3. Anthropometric parameters and Imatinib-related toxicities

Overall, 8 (57.1%) patients experienced at least one Imatinib-related toxicity within the first 6 months of therapy; 2 (14.3%) had grade 1 toxicity; 2 (14.3%) had grade 2 and 4 (28.6%) reported grade 3 events; diarrhea was the most common toxicity of any grade, being reported in 5 out of the 8 patients which suffered from drug related adverse events (AE). Globally, 3 patients had 2 or more toxicities. No grade 4 or 5 toxicities occurred. All the patients who experienced grade 3 adverse events were prescribed with a reduced dosage (300 mg). No correlation between any grade toxicities and BMI, BMD, SMI and LBM was found. Similarly, none of the anthropometric parameters was related to the type or the number of AEs. However, patients who suffered from grade 3 AEs within the first 6 months of therapy had a significantly lower

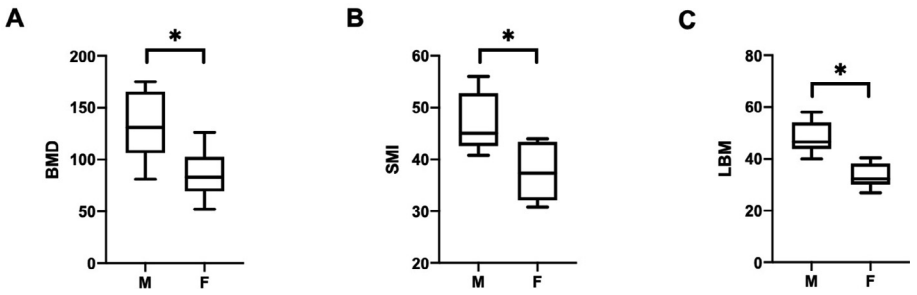

Fig. 2. (A) Differences in BMD according to gender in cases (p = 0.013). (B) Differences in SMI according to gender in cases (p = 0.018). (C) Differences in LBM according to gender in cases (p = 0.001).

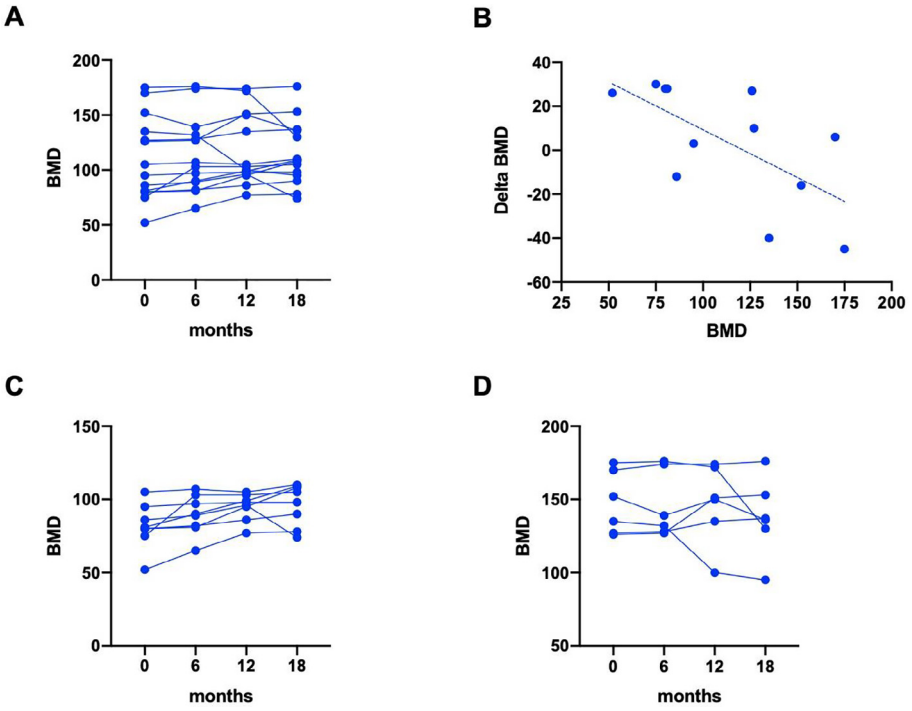

Fig. 3. (A) BMD trend from baseline to 18 months of follow-up in the whole population of cases (p = 0.021). (B) Correlation between the differences (delta) of BMD and baseline values in cases (p = 0.021, r = -0.653, r^2 = 0.426). (C; D) BMD trend from baseline to 18 months of follow-up in patients with basal BMD < 120 mg/cm^3 (p = 0.002) and ≥ 120 mg/cm^3 (p = 0.993) respectively.

Table 2
Baseline characteristics in patients with low and high BMD.

	Patients with basal BMD < 120 mg/cm^3	Control group with basal BMD < 120 mg/cm3	Differences
Number	8	8	N/A
Age Median; (Range)	69.2; (35.9–77.4) y	70.4; (61.9–75.6) y	p > 0.05
Gender N (%)	5F (62.5%), 3 M (37.5%)	4F (50%%), 4 M (50%)	p > 0.05
BMI Median; (Range)	23.9; (17.8–27.7) kg/m^2	24.6; (17.3–31.8) kg/m^2	p > 0.05
BMD Median; (Range)	83.5; (52–110) mg/cm^3	83; (59–119) mg/cm^3	p > 0.05
SMI Median; (Range)	42.9; (30.8–46.2) cm/m^2	38.2; (32.7–64) cm/m^2	p > 0.05
LBM Median; (Range)	34.9; (26.8–46.1) kg	34.4; (31.5–68.3) kg	p > 0.05

baseline BMI (median: 22.5 vs 25.8: p = 0.014) and LBM (median: 34.2 vs 44.3: p = 0.024) (Fig. 4) compared to the rest of the population. There also was a non-significant trend between basal BMD and grade 3 toxicities (p = 0.060).

4. Discussion

This is the first paper to investigate the impact of Imatinib on BMD, SMI and LBM in GIST patients treated in the adjuvant setting, therefore without the confounding factors potentially related to metastatic disease. In our cohort, men reported higher BMD, SMI and LBM at baseline. We found a positive correlation between BMD and both SMI and LBM. On the contrary, BMI, age and site of the primary tumor did not influence BMD, SMI and LBM. These findings are consistent with epidemiological data, which clearly report higher incidence of osteoporosis and osteopenia in post-menopausal women [18].

Similarly, there is compelling evidence about the close interaction between bone and muscle [10] and this would explain the correlation between BMD, SMI and LBM. BMD and SMI are known to decrease with age [19], however we did not find any correlation between these variables. This could be explained by the relatively high median age of our sample, which could also justify the high incidence of osteopenia.

Table 3
Baseline characteristics in patients with low BMD and control group.

	Patients with basal BMD < 120 mg/cm^3	Control group with basal BMD < 120 mg/cm3	Differences
Number	8	8	N/A
Age Median; (Range)	69.2; (35.9–77.4) y	70.4; (61.9–75.6) y	p > 0.05
Gender N (%)	5F (62.5%), 3 M (37.5%)	4F (50%%), 4 M (50%)	p > 0.05
BMI Median; (Range)	23.9; (17.8–27.7) kg/m^2	24.6; (17.3–31.8) kg/m^2	p > 0.05
BMD Median; (Range)	83.5; (52–110) mg/cm^3	83; (59–119) mg/cm^3	p > 0.05
SMI Median; (Range)	42.9; (30.8–46.2) cm/m^2	38.2; (32.7–64) cm/m^2	p > 0.05
LBM Median; (Range)	34.9; (26.8–46.1) kg	34.4; (31.5–68.3) kg	p > 0.05

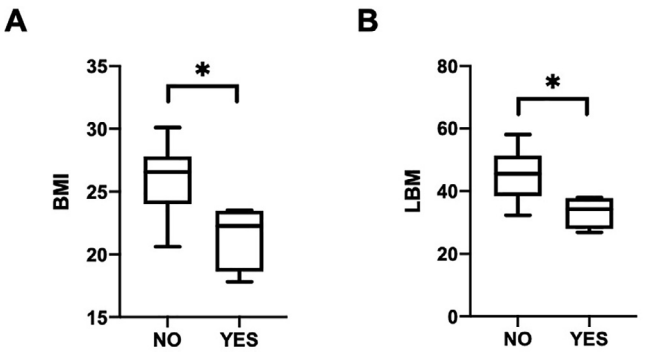

Fig. 4. (A) Differences in basal BMI between patients who did not and who did experience grade 3 adverse events (p = 0.014). (B) Differences in basal LBM between patients who did not and who did experience grade 3 adverse events (p = 0.024).

The therapy with Imatinib led to a significant increase in BMD in patients with low basal value and it did not influence other anthropometric parameters. The effect of Imatinib in bone metabolism has been previously reported and it is thought to be mainly caused by Imatinib-mediated inhibition of PDGFR [5]. Berman et al. [20] reported changes in serum markers of bone metabolism in patients treated with Imatinib for CML or GIST and they inferred a possible role of Imatinib in inhibiting bone remodeling; however they did not correlate serum markers with bone density data [20]. Later, Vandyke et al. [8] investigated bone metabolism parameters, bone biopsy and DXA findings in a cohort of 11 patients affected by CML and treated with high-dose Imatinib. Interestingly, markers of osteoclast activity dropped during treatment whereas trabecular bone volume and trabecular thickness increased during the first 24 months of therapy. These changes were confirmed by biopsy specimens which showed a decrease in osteoclast number but no effect on osteoblasts. However, it is worth noting that all the patients achieved a complete cytogenetic remission which could have contributed to bone changes. In the same setting, Hoehn et al. [21] confirmed the above findings, and they found no correlation between bone density and clinical or cytogenetic response; supporting the direct effect of Imatinib on bone metabolism.

Moreover, pre-clinical models confirmed the modulatory activity of Imatinib on bone cells. In particular, it was described to promote the apoptosis of osteoclasts and to inhibit their differentiation [6], while stimulating osteoblasts [5] with consequent bone mineralization. The effect on osteoblasts was however reported to decrease over time [5]. The increase in BMD that we observed is in keeping with the above findings and the results are further strengthened by the presence of a control group. The fact that only patients with low basal BMD experienced an increase in bone density could be related to the prominent activity of osteoclast typical of osteoporosis and osteopenia [22], although it remains to be understood why some patients with normal BMD at baseline reported a downward non significant trend. Moreover, the effect of Imatinib on bone cells is mainly mediated by PDGFR inhibition [5], which exerts its activity on osteoclast, blocking resorption more than increasing bone formation [23]. As a consequence of the above evidence, we could infer that the Imatinib-mediated inhibition of bone resorption is more evident in case of predominant osteoclast activity as osteoporosis and osteopenia. In patients with normal mineral density it is present a stable equilibrium between bone resorption and formation, thus the final effects of Imatinib could be less evident. A long exposure to Imatinib might paradoxically result in a reduction in BMD, as the transient stimulation on osteoblast activity subsequently decreases to levels at, or lower than, those at baseline over time [24].

In 2015, Moryoussef et al. [9] reported a positive effect of Imatinib on muscle composition in patients treated with Imatinib in both adjuvant and metastatic setting. In fact, 11 out of 12 sarcopenic patients reported reversal of sarcopenia after 6 months of treatment. Differently from the above, we did not find any changes in muscle status during Imatinib therapy. We identified few reasons for this discordance. Firstly, we focused on the adjuvant setting, whereas in the study by Moryoussef et al., most of the sarcopenic patients had advanced GIST and it would be hard to define whether the effect on muscle was directly related to Imatinib or secondary to its reduction of tumor burden. Secondly, due to the small size of our sample and to the specific setting, the incidence of sarcopenia was relatively low, and this could have masked any potential impact of Imatinib; therefore our results on SMI modifications should be taken with caution.

We have described an association between BMI, LBM and drug-related adverse events. This correlation has already been reported in patients receiving TKIs or other anticancer agents for various malignancies [9,25]. In particular, we found that development of grade 3 toxicities was more common in patients with low BMI and low LBM. This association has been described, among others,

in patients receiving Sunitinib for renal cell carcinoma [25] and in patients treated with Sorafenib for advanced hepatocellular carcinoma [26]. Low LBM and low BMI could result in impaired distribution with higher drug exposure [27]. This effect is more evident for molecules with high albumin binding as Sorafenib [28], Epirubicin [27] and Imatinib, which is about 95% bound to plasma protein [29]. However, in sarcopenic patients receiving Imatinib this hypothesis has not been specifically tested in pharmacokinetics studies. In the cohort of GISTs patients analyzed by Moryoussef et al. [9], anemia and fatigue were more common in sarcopenic patients, but the direct association with BMI was not investigated, even though to assess the sarcopenic status they adopted Martin's formula, which includes BMI [30].

According to recent studies, CT scan has high accuracy in the evaluation of bone density [14], this aspect, along with the monocentric imaging evaluation, confers quality to our series. However, it should be reported that our study has several limitations. First of all, the limited sample size does not allow us to outline definitive conclusions. Secondly, due to the retrospective nature of the study, we did not have data about imatinib pharmacokinetics nor serum markers of bone metabolism, e.g. calcium, PTH, vitamin D and phosphate, which are not routinely tested in this clinical setting. Differently from previous studies conducted in CML, where bone biopsies are part of the routinary management of patients, histological data to confirm the changes in bone density were not collected in our study, and are unlikely to be reported in the future in this setting.

In conclusion, we demonstrated for the first time that adjuvant Imatinib may have a positive impact on BMD, in particular in the case of low baseline values. Furthermore, we confirmed the role of body composition in influencing drug-related toxicities. Larger prospective trials with metabolic, pharmacokinetics and quality of life evaluations would be warranted to consolidate our findings, which could have implications for the management of patients receiving Imatinib as a precautional treatment.

CRediT authorship contribution statement

Claudia Angela Maria Fulgenzi: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Andrea Napolitano:** Formal analysis, Writing – original draft, Writing – review & editing. **Eliodoro Faiella:** Data curation. **Laura Messina:** Data curation. **Gennaro Castiello:** Data curation. **Flavia Paternostro:** Data curation. **Marianna Silletta:** Supervision. **Francesco Pantano:** Supervision. **Giuseppe Tonini:** Supervision. **Daniele Santini:** Supervision, Writing – review & editing. **Bruno Vincenzi:** Conceptualization, Supervision, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbo.2022.100422.

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