

# Reversible sarcopenia in patients with gastrointestinal stromal tumor treated with imatinib

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## Abstract

**Background** Imatinib is a long-term, oral, targeted therapy for high-risk resected and advanced gastrointestinal stromal tumours (GIST). It is known that sarcopenia affects prognosis and treatment tolerance in patients with various solid cancers. We analysed lumbar skeletal muscle index changes in imatinib-treated GIST patients. Imatinib tolerance was also assessed to evaluate the influence of pre-treatment sarcopenia.

**Methods** Thirty-one patients with advanced ( $n = 16$ ) or high-risk resected ( $n = 15$ ) GIST treated with imatinib (400 mg/day) were analysed retrospectively. Lumbar skeletal muscle indexes were evaluated on computed tomography images obtained before starting imatinib for all patients and at 6 months for those initially sarcopenic. Sarcopenia was defined using consensual cutoffs. Imatinib-induced toxicities were assessed after 3 months of administration.

**Results** Twelve (38.7%) of the 31 patients were sarcopenic, including one unassessable at 6 months. Seven (63.6%) of the 11 assessable sarcopenic patients became non-sarcopenic after 6 months of imatinib. Pre-treatment sarcopenia was not associated with grades 3–4 toxicities, but the mean number of all-grade toxicities per sarcopenic patient was significantly higher for those non-sarcopenic (4.1 vs. 1.7, respectively,  $p < 0.01$ ) after 3 months of treatment. Grades 1–2 anaemia and grades 1–2 fatigue were more frequent for sarcopenic than non-sarcopenic patients (83% vs. 26%,  $P < 0.01$  and 42% vs. 5%,  $P = 0.02$ , respectively).

**Conclusions** Sarcopenia is reversible in some GIST patients treated with imatinib. Pre-imatinib sarcopenia is predictive of non-severe toxicities, particularly anaemia and fatigue.

**Keywords** Imatinib; C-kit inhibitors; Sarcopenia; Gastrointestinal stromal tumours; Toxicity; Body composition

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## Introduction

The paradigm and treatment of advanced gastrointestinal stromal tumours (GIST) has shifted since the arrival of targeted therapies.<sup>1</sup> Imatinib is an active multikinase inhibitor that mainly targets C-kit tyrosine-kinase receptors and the platelet-derived growth factor receptor. Imatinib use has been validated for adjuvant and palliative therapy settings.<sup>2</sup> Imatinib is generally well-tolerated and known to improve

performance status (PS),<sup>1</sup> but up to 16% grades 3–4 toxicities, leading to at least 40% withdrawals, have been reported.<sup>3</sup>

Cancer cachexia is a syndrome of body mass loss after accelerated catabolism of fat and skeletal muscle described as sarcopenia and anorexia.<sup>4</sup> In the elderly, sarcopenia or low muscle mass is known to increase morbidity, healthcare costs, and mortality.<sup>5</sup> Sarcopenia affects 50–90% of untreated cancer patients.<sup>6</sup> Recently, in oncology, sarcopenia was shown to be a predictor of severe toxicity patients included in phase 1 trials,

suggesting that it should be considered an inclusion criterion for such studies.<sup>7</sup> Sarcopenic patients had low PS, shorter survival, more chemotherapy toxicities and post-operative infections, and longer post-operative hospitalization times.<sup>8–17</sup> In addition, exposure to tyrosine-kinase inhibitors (e.g. sorafenib or sunitinib) has been associated with dose-limiting toxicity (DLT) in patients with renal cell or hepatocellular carcinomas.<sup>18–20</sup> Computed tomography (CT) scans acquired during routine care have been validated as an accurate and robust imaging technique to evaluate sarcopenia in cancer patients.<sup>21</sup>

We hypothesized that sarcopenia, like PS previously, could change under imatinib administration, especially because toxicities are thought to be more severe in this population. Should sarcopenia prove to be reversible and a factor predictive of toxicities, identifying and managing it in GIST patients to be treated with imatinib will be important. Thus, our aim was two-fold: first, to assess the influence of imatinib on sarcopenia and, second, to compare imatinib-induced toxicities between patients with and without pre-treatment sarcopenia.

## Materials and methods

### Study design

This retrospective study included all consecutive patients treated with imatinib for advanced or high-risk resected GIST, from 1 January 2005 to 31 December 2013, in three French referral centres (Reims University Hospital, Cochin University Hospital, and Rambouillet Hospital). Electronic and paper charts were reviewed. The local ethics committee (Reims Institutional Review Board) approved the study, in accordance with the Declaration of Helsinki.

### Patients and treatment

Patients were enrolled when they fulfilled the following inclusion criteria: histologically proven GIST, imatinib prescribed at a fixed dose of 400 mg/day, at least 6 months of follow-up, and age >18 years old. Patients who did not have CT imaging within the 30 days preceding treatment onset or those who did not have continuous follow-up in one of the three referral centres were excluded. Patients had to be naïve for all other anticancer therapies.

### Demographic data and anthropometric measurements

Demographic data (age, sex, and PS), tumour characteristics, therapy setting (adjuvant or palliative), height, and weight

were collected from medical records onto predefined data forms. Patients were weighed at treatment onset and 3 and 6 months thereafter. Weight and height were measured according to standard methods.

### Toxicity assessment

Toxicity was assessed 3 months after starting imatinib. All side effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0,<sup>22</sup> during routine follow-up consultations by experienced physicians and recorded in patients' medical files. Those doctors were unaware of the patient's sarcopenia status. The imatinib dose was lowered for grade 3 toxicity and stopped for grade 4 toxicity. A DLT was defined as any toxicity leading to treatment modification (reduction or withdrawal). Toxicity was evaluated by reviewing the patients' medical charts.

### Computed tomography imaging and body composition assessments

Body mass index (BMI) was calculated [weight (kg)/height (m<sup>2</sup>)]. Regional muscle tissue was retrospectively evaluated on CT images, obtained during the 30 days preceding imatinib onset, and after 6 months of treatment for those initially sarcopenic, as schematized in *Figure 1*, by radiologists unaware of the toxicity assessment. Between treatment onset and the 6 months of follow-up on CT scan, each patient's nutritional and exercise programmes remained unchanged. ImageJ software v1.46r (National Institutes of Health) was used (*Figure 2*). Body composition was calculated twice: during the 30 days before starting imatinib and after 6 months of intake for initially sarcopenic patients.

The third lumbar vertebra (L3) was chosen as the standard landmark. Two consecutive images between L3 and the iliac crest were examined. Muscles were identified by a trained radiologist according to anatomical features and pre-established Hounsfield unit thresholds (from –29 to +150) for skeletal muscles.<sup>23</sup> For each patient, the psoas, paraspinal, and abdominal wall muscles were measured, cross-sectional areas (cm<sup>2</sup>) of the sum of all these muscles were calculated for each image, and the mean value for the two consecutive images was calculated. This value is linearly related to whole body muscle mass.<sup>24</sup> It was then normalized to height, as for BMI and other body composition components, and expressed in square centimetre per square metre.

As defined by Martin *et al.*, patients were considered sarcopenic when their lumbar skeletal muscle index (skeletal muscle area at L3 divided by height squared) is as follows: for men, <53 cm<sup>2</sup>/m<sup>2</sup> with BMI >25 kg/m<sup>2</sup> and <43 cm<sup>2</sup>/m<sup>2</sup> with BMI <25 kg/m<sup>2</sup> and for women, <41 cm<sup>2</sup>/m<sup>2</sup> with any BMI.<sup>25</sup> Estimated lean body mass (LBM) and estimated whole

Figure 1 Study timelines as a function of sarcopenia status.

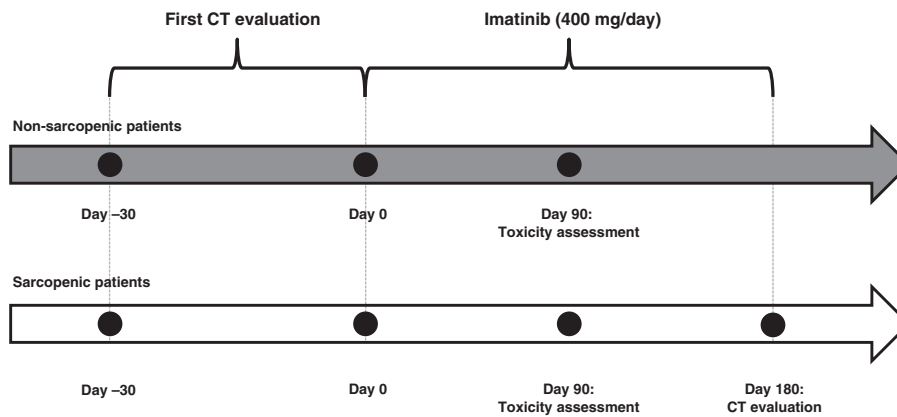
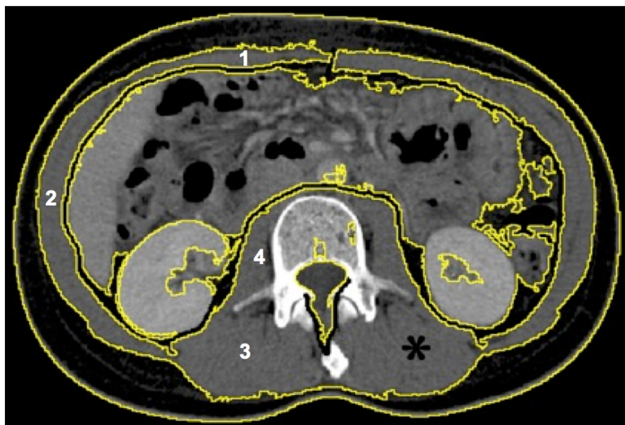


Figure 2 Selection of lumbar muscle areas [\* : regions of interest corresponding to rectus, oblique, and lateral abdominal (1 and 2); paraspinal (3); and psoas muscles (4)] with specific thresholds. Image from ImageJ software.



body skeletal muscle mass (SMM) were calculated from muscle cross-sectional areas, according to regression equations of Moutzarkis *et al.*<sup>21</sup> and Shen *et al.*,<sup>21,24</sup> respectively.

### Statistical analyses

Quantitative variables are expressed as means [standard deviation (SD)] and qualitative data as numbers (%). Pre-imatinib characteristics and imatinib-related toxicities were compared between sarcopenic and non-sarcopenic patients in univariate analyses using Student's *t*-test (for continuous variables) or Fisher's exact test (for qualitative variables). Weights, BMIs, and lumbar skeletal muscle indexes were compared before and after 6 months of treatment using Student's *t*-test. A *P*-value of <0.05 defined significance. All statistical tests were computed with BiostaTGV (<http://marne.u707.jussieu.fr/biostatgv/>).

## Results

### Baseline demographic, tumour, and anthropometric data

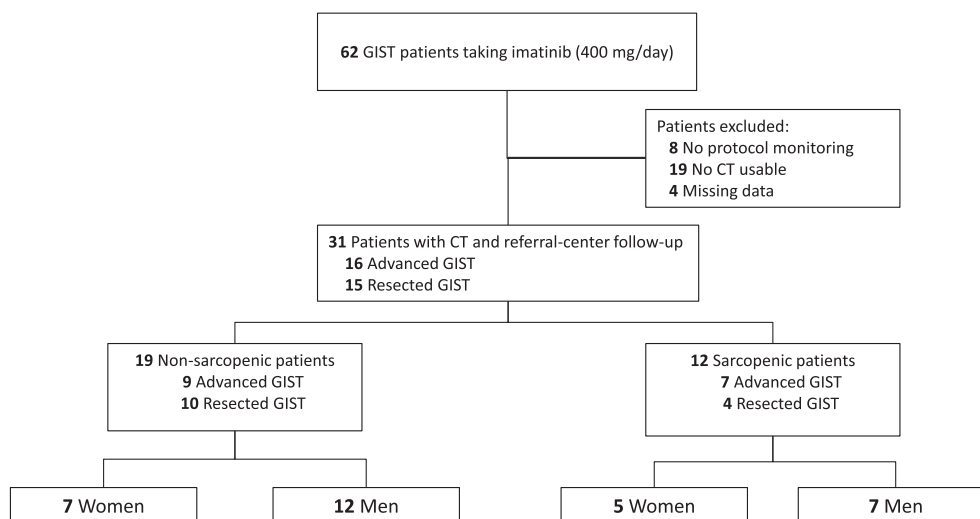
Among the 62 consecutive imatinib-treated GIST patients, 31 were excluded because follow-up monitoring was not conducted in one of the three referral centres ( $n=8$ ), no CT was available or achieved within the 30 days preceding imatinib onset or analyzable ( $n=19$ ), or height was missing ( $n=4$ ). Thus, 31 patients [13 women and 18 men, mean (standard deviation) age of 62.7 (12.3) years, with advanced ( $n=16$ ) or high-risk resected ( $n=15$ ) GIST] were finally included, as shown in the patient flow chart (Figure 3). Patients treated in an adjuvant setting had a minimum of 18 days between surgery and LBM estimations. Pre-treatment body composition, demographic, and tumour characteristics according to sarcopenia status are reported in Table 1.

Among the 31 studied patients, 12 (38.7%) were sarcopenic. Sarcopenic patients differed significantly from non-sarcopenic patients, as expected, for weight ( $P=0.03$ ), estimated whole LBM ( $P=0.004$ ), and lumbar skeletal muscle index ( $P<0.001$ ). No differences were observed for PS, age, height and BMI, tumour characteristics, or therapy settings.

### Imatinib impact on sarcopenia

Among the 12 sarcopenic patients, one could not be evaluated at 6 months (no CT). Their pre-treatment mean weight, BMI, and lumbar skeletal muscle index (SD), respectively, were 66.4 ( $\pm 13.1$ ) kg, 23.2 ( $\pm 3$ ) kg/m<sup>2</sup>, and 41.8 ( $\pm 5.1$ ) cm<sup>2</sup>/m<sup>2</sup>. After 6 months of imatinib administration, their mean values had not changed significantly: weight [65.0 ( $\pm 11.2$ ) kg;  $P=0.78$ ], BMI [22.8 ( $\pm 2.9$ ) kg/m<sup>2</sup>;  $P=0.96$ ], and lumbar skeletal muscle index [46.4 ( $\pm 6.2$ ) cm<sup>2</sup>/m<sup>2</sup>;  $P=0.058$ ]. Notably, according to computations with the methods of Moutzarkis *et al.* for

Figure 3 Patient flow chart: patient identification, inclusion, and exclusion.



estimated LBM<sup>21</sup> and Shen *et al.* for estimated whole body SMM,<sup>24</sup> respectively, after 6 months of imatinib, patients had estimated gains of +4.15 kg (i.e. 2.3 kg/100 days) and +2.3 kg (i.e. +1.27 kg/100 days).

Among the 12 initially assessable sarcopenic patients, seven (63.6%) of the 11 that could be evaluated after 6 months of treatment had become non-sarcopenic, including five (71.4%) out of seven with advanced GIST and two (50%) out of four with high-risk resected GIST.

### Baseline sarcopenia and imatinib-induced toxicities

Toxicities occurring in the entire population and comparison between sarcopenic and non-sarcopenic patients are reported in *Table 2*.

Any grade toxicities did not differ between sarcopenic and non-sarcopenic patients during the first 3 months of imatinib. No grades 3–4 toxicity and no DLT occurred in our population. No treatment-related death was observed. Sarcopenic patients had significantly higher mean (SD) numbers of toxicities per patient than non-sarcopenic patients within the first 3 months ( $P=0.003$ ). Those toxicities were only grades 1–2 toxicities.

Anaemia and fatigue were the only specific toxicities, observed significantly more frequently in sarcopenic than non-sarcopenic patients ( $P<0.01$  and  $P=0.02$ , respectively). No significant difference was found for the other most frequent toxicities.

## Discussion

This is the first study, to our knowledge, to evaluate sarcopenia in GIST patients. Sarcopenia, identified in 38.7%

of patients, had been reversed after 6 months of imatinib in 63.6% of them. Moreover, although sarcopenia was predictive of more numerous toxicities per patient grades 1–2, our results indicated that pre-imatinib sarcopenia did not correspond to more severe toxicities. Sarcopenic patients experienced significantly more anaemia and fatigue.

Evaluated in various solid tumours (e.g. digestive malignancies, breast cancers, respiratory tract cancers, and renal cell carcinomas), sarcopenia was found to be either predictive of DLT or a prognostic factor of survival.<sup>9,12–20,26,27</sup> Sarcopenia in GIST merits being screened because a well-tolerated, long-term, effective, oral treatment is available. Furthermore, because imatinib improved PS, studying the underlying affect of sarcopenia was relevant.<sup>1</sup>

Our results identified ~40% sarcopenic GIST patients. This frequency agrees with other gastroenterology studies, which found 15–50%.<sup>9,12,16,18,26,27</sup> Sarcopenia should be sought, as it is known to be a negative independent prognostic factor of shorter survival and low PS for patient with solid tumours<sup>9,16,17</sup> and predictive of toxicity.<sup>8</sup> Martin *et al.* showed that skeletal muscle depletion was a powerful prognostic factor and, in 2013, proposed new sex-specific cutoffs according to BMI thresholds associated with shorter survival (BMI = 25 kg/m<sup>2</sup>) to stage patients with pre-cachexia, cachexia, or refractory cachexia.<sup>25,28</sup>

Herein, 63.6% of initially sarcopenic patients became non-sarcopenic after 6 months of imatinib. This reversal might be explained by the drug's anti-tumour activity, with improved PS after several months of administration, as reported by Demetri *et al.*,<sup>1</sup> which may result in an increased food intake. Other explanations could be found in molecular pathways through interleukin-6 and nuclear factor- $\kappa$ B, which inhibit muscle synthesis by mediating inflammation that was attenuated by imatinib in humans.<sup>4,29,30</sup> Our findings were not

**Table 1 Comparison of baseline demographic, anthropometric, and tumour characteristics between sarcopenic and non-sarcopenic patients**

Characteristics	Patients			P-value
	All	Non-sarcopenic	Sarcopenic	
Patients, <i>n</i>	31	19	12	
Sex, <i>n</i> (%)				
Women	12 (38.7)	7 (36.8)	5 (41.7)	1
Men	19 (61.3)	12 (63.2)	7 (58.3)	
Age, mean (SD) <sup>a</sup>	62.7 (12.3)	62.7 (9.8)	64.1 (15.9)	0.63
Performance status, <i>n</i> (%)				
0	11 (35.5)	9 (47.4)	2 (17/16.7)	0.2
1	18 (58.1)	9 (47.4)	9 (75)	
>1	2 (6.5)	1 (5.3)	1 (8.3)	
Weight, mean (SD) <sup>a</sup> (kg)	74.3 (18.2)	79.3 (19.6)	66.4 (12.6)	0.03
Height, mean (SD) <sup>a</sup> (cm)	167.3 (9.2)	169.1 (9.2)	169 (9.4)	0.96
BMI, mean (SD) <sup>a</sup> (kg/m <sup>2</sup> )	26.3 (5)	27.4 (4.9)	24.6 (4.8)	0.11
Lumbar SMI <sup>a</sup> , mean (SD) <sup>a</sup> (cm <sup>2</sup> /m <sup>2</sup> )	50.2 (10.7)	54.4 (10.7)	42 (5.2)	<0.001
Estimated whole LBM, mean (SD) <sup>a</sup> (kg)	44.6 (11.6)	49.2 (12.3)	38.4 (6.6)	0.004
Tumour				
Localization, <i>n</i> (%)				
Gastric	18 (58.1)	13 (68.4)	6 (50)	0.22
Duodenal	6 (19.4)	2 (10.5)	4 (33.3)	
Jejunal	5 (16.1)	4 (21.1)	1 (8.3)	
Rectum	0	0	0	
Other	1 (3.2)	0	1 (8.3)	
Macroscopic size, <i>n</i> (%)				
<2 cm	1 (3.2)	1 (5.3)	0	0.3
2–5 cm	4 (12.9)	4 (21.1)	0	
5–10 cm	7 (22.6)	3 (15.8)	4 (33.3)	
>10 cm	19 (61.3)	11 (57.9)	8 (66.7)	
Mitotic index, <i>n</i> (%)				
<5%	6 (19.4)	4 (21.1)	2 (16.7)	1
5–10%	8 (25.8)	5 (26.3)	3 (25)	
>10%	17 (54.8)	10 (52.6)	7 (58.3)	
Genotype, <i>n</i> (%)				
Exon 11	14 (45.2)	8 (42.1)	6 (50)	0.62
Exon 9	1 (3.2)	1 (5.3)	0	
Exon 18	3 (9.7)	3 (15.8)	0	
D842v	4 (12.9)	2 (10.5)	2 (16.7)	
Unknown	9 (29.0)	5 (26.3)	4 (33.3)	
Perforation, <i>n</i> (%)	6 (19.4)	4 (21.1)	2 (16.7)	0.6
Therapy setting, <i>n</i> (%)				
High-risk resected GIST	15 (48.4)	10 (52.6)	5 (41.7)	1
Advanced GIST	16 (51.6)	9 (47.4)	7 (58.3)	

SD, standard deviation; LBM, lean body mass; GIST, gastrointestinal stromal tumours.

<sup>a</sup>SMI, skeletal muscle index.

consistent with those of the three studies assessing that muscle loss increases under treatment. Antoun *et al.*<sup>31</sup> reported that sorafenib exacerbated muscle loss in patients with renal cell carcinomas. In a study with temsirolimus, all patients with various advanced solid tumours that had been sarcopenic at baseline remained so after 2 months (but the follow-up was perhaps not sufficiently long to detect such modifications).<sup>32</sup> Interestingly, it was previously shown in patients with advanced cholangiocarcinomas that selumetinib, an inhibitor of interleukin-6 secretion (like imatinib), promoted muscle gain compared with standard therapy, with a +2.3 kg estimated whole body SMM increase after 100 treatment days (calculated with the method of Shen *et al.*).<sup>33</sup> That gain was superior to the present study with imatinib (+1.27 kg), probably because of selumetinib's more specific action against muscle wasting. Nevertheless, our findings

suggest that imatinib might not only improve GIST prognosis because of its anti-tumour activity but also improve body composition and down-regulating inflammation. They indicate that imatinib might even be beneficial for patients with low PS and sarcopenia; however, that possibility remains to be confirmed in larger studies.

No grades 3–4 toxicities and no DLT had been observed within 3 months of treatment whatever body composition in contrast to the observations made previously with sarcopenic patients who experienced more severe toxicities (digestive cancer and various cytotoxic chemotherapies,<sup>14,26,27</sup> metastatic breast cancer and capecitabine;<sup>13</sup> renal cell carcinoma and sunitinib or sorafenib,<sup>15,19,20</sup> and hepatocellular carcinoma and sorafenib<sup>18</sup>). This difference could be explained by imatinib's highly selective mechanism of action that inhibits intracellular abelson (ABL) kinase, the transmembrane

**Table 2** Comparison of toxicities between sarcopenic and non-sarcopenic patients

Characteristics	Patients			P-value
	All	Non-sarcopenic	Sarcopenic	
Patients, <i>n</i>	31	19	12	
Day 1 to month 3, toxicity, <i>n</i> (%)				
Any grade	26 (83.9)	14 (73.7)	12 (100)	0.13
Grades 1–2	26 (83.9)	14 (73.7)	12 (100)	0.13
Grades 3–4	0	0	0	—
Toxicities per patient, mean (SD)	2.6 (2.2)	1.7 (1.8)	4.1 (1.9)	<0.01
Toxicity, all grades, <i>n</i> (%)				
Fatigue	6 (19.4)	1 (5.3)	5 (41.7)	0.02
Myalgias	4 (12.9)	2 (10.5)	2 (16.7)	0.6
Arthralgias	3 (9.6)	1 (5.3)	2 (16.7)	0.54
Oedema	16 (51.6)	8 (42.1)	9 (75)	0.27
Rash	2 (6.5)	2 (10.5)	0	0.5
Pruritus	5 (16.3)	2 (10.5)	3 (25)	1
Xerosis	7 (22.6)	4 (21.1)	3 (25)	1
Conjunctivitis	2 (6.5)	2 (10.5)	0	0.5
Nausea	2 (6.5)	1 (5.3)	1 (8.3)	1
Diarrhoea	8 (25.8)	3 (15.8)	5 (41.7)	0.2
Vomiting	2 (6.5)	1 (5.3)	1 (8.3)	1
Anaemia	15 (48.4)	5 (26.3)	10 (83.3)	<0.01
Neutropenia	5 (16.3)	2 (10.5)	3 (25)	0.65
Thrombocytopenia	1 (3.2)	0	1 (8.3)	0.39

SD, standard deviation.

receptor C-kit, platelet-derived growth factor receptor,<sup>1</sup> and kit autophosphorylation and activation of mitogen-activated protein kinase. Pre-treatment sarcopenia did not correspond to more severe toxicity in the only study that treated various solid tumours with temsirolimus.<sup>32</sup> Our results suggested that sarcopenia was not predictive of severe imatinib toxicity.

Sarcopenic patients experienced more numerous non-severe toxicities than non-sarcopenic patients, especially anaemia and fatigue. Several explanations may be advanced. First, sarcopenic patients had lower volumes of distribution reflecting their low estimated LBM.<sup>10</sup> Direct consequences of lower estimated LBM are higher blood drug concentrations over a shorter period and less drug clearance from the systemic circulation.<sup>10,13</sup> Second, systemic inflammation, which underlies sarcopenia, could inhibit cytochrome *P*<sub>450</sub> 3A4 (CYP3A4) activity and lead to drug toxicities because C-kit inhibitors are eliminated with CYP3A4.<sup>9,18,28,34</sup> Moreover, systemic inflammation can explain higher prevalence of anaemia (with fatigue associated) in sarcopenic patients. Cancer anorexia, leading to sarcopenia, is also responsible of vitamin B<sub>12</sub>, folate, and iron deficiencies explaining anaemia. The potential role of anaemia and gastrectomy merits being explored, but gastric GIST localization in our patients was not more frequent in the sarcopenic than non-sarcopenic group (50% vs. 68%, respectively). Interestingly, as a self-maintaining process, it has been previously described that anaemia increased muscle loss in pancreatic cancer patients<sup>35</sup> confirming that anaemia and cachexia are usually associated, and that anaemia is one of the biochemical markers used to diagnose cachexia.<sup>36</sup>

Since most grades 1–2 toxicities impair the patient's quality of life and, thus, compliance with long-term therapy, early managing those toxicities appears to be an essential

therapeutic endpoint. Indeed, the tumour can progress rapidly as soon as the patient stops treatment.<sup>1,2</sup> Once sarcopenia is identified, physicians should insist on treatment adherence and reinforce it with educational consultations with specifically trained nurses. An international consensus was reached to define the cachexia phenotype (reduced food intake, hyper-catabolism, and evaluation of muscle mass and quality of life consequences), and to integrate cachectic patients into a multimodal nutrition plan, comprising exercise, nutrition and anti-inflammatory agents.<sup>28,37</sup> Some specific drugs and anti-cachexia drugs have been studied.<sup>38,39</sup>

This study has several limitations. First, the small number of patients included, which merely reflects the rarity of GIST, some missing initial data and could explain the absence of grades 3–4 toxicities in the first 3 months of treatment. Second, sarcopenia reversibility could have been biased because the study was not randomized, and resected and advanced GIST were analysed together to try to overcome the small sample size. Among the seven sarcopenic patients with advanced GIST, sarcopenia was reversed in five (71.4%), but all tumour responses were not available. Indeed, we could not prove that the sarcopenia reversal in the resected GIST patients was not only a consequence of the primary resection.

In conclusion, sarcopenia was reversible in some GIST patients treated with imatinib. Sarcopenia was significantly associated with a higher mean number of non-severe toxicities patient (in particular anaemia and fatigue). These results confirm that imatinib administration could be safe in patients with poor condition. Management of early sarcopenia to avoid failed treatment adherence seems crucial because sarcopenia tended to disappear during the first 6 months of imatinib administration.

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*Sarcopenia and Muscle. J Cachexia Sarcopenia Muscle* 2010;1:7–8). No funding was received to support this work.

## Conflict of interest

R.C. and O.B. are orators/consultants for Novartis. F.M., M.D., J.V., C. Brezault, C. Barbe and C.H. declare that they have no conflicts of interest.

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