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Low body weight and body mass index may be associated with musculoskeletal pain following imatinib discontinuation in chronic myeloid leukemia

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ABSTRACT

It is difficult to predict musculoskeletal pain as a withdrawal syndrome following the discontinuation of imatinib (IM) in patients with chronic myeloid leukemia. We investigated a link between physical size and musculoskeletal pain following IM discontinuation. In total, seven out of 24 patients developed musculoskeletal pain after discontinuing IM. Those with symptoms had a significantly lower body weight (BW) and body mass index (BMI) than those without symptoms. While previous reports indicated that physical size is associated with the pharmacokinetics of IM, our current study suggests that lower BW and BMI may be associated with musculoskeletal pain following IM discontinuation.

1. Introduction

Tyrosine kinase inhibitors (TKIs) such as imatinib (IM) can dramatically improve the prognosis of patients with chronic myeloid leukemia (CML), and some patients showing a deep molecular response (DMR) can attempt to discontinue IM treatment. [1] However, Richter et al. previously reported that musculoskeletal pain can occur in association with the withdrawal of IM. [2] In a previous imatinib suspension and validation (ISAV) study, analysis of the quality of life showed a trend towards increased pain score following the cessation of IM [3]. Furthermore, Lee et al. showed that 30% of patients who discontinued IM developed musculoskeletal pain or pruritus in the Korean Imatinib Discontinuation (KID) study [4].

In an earlier study, we used a questionnaire to assess musculoskeletal pain in patients with CML who had achieved DMR ($MR^{4.0}$) and discontinued TKI treatment, including IM, nilotinib, and dasatinib [5]. Nine out of the 27 patients surveyed developed musculoskeletal pain after discontinuing TKIs. In the present study, we investigated whether there was an association between physical size and musculoskeletal pain in patients following the discontinuation of IM treatment.

2. Materials and methods

This study was approved by the Institutional Review Board of Tokyo Medical University (No. 3052) and involved additional analysis of data acquired from IM discontinuation patients who had completed a questionnaire in a previous study [5]. In the questionnaire, participants were asked whether they had developed musculoskeletal pain during TKI therapy and after TKI cessation. The participants with musculoskeletal pain were asked to describe the location, severity, and duration of symptoms, the time taken to experience symptoms following the discontinuation of TKIs, and the type of treatment (Table 1). Symptom severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0). We evaluated several factors including sex, age, Sokal category, history of interferon-α, duration of TKI therapy, time to achieve DMR, duration of DMR, electrolyte abnormalities (Na^+, K^+, Ca^{2+}), along with creatine phosphokinase (CPK) and C-reactive protein (CRP) concentrations. TKIs were restarted in patients who experienced a loss of major molecular response ($MR^{3.0}$).

We also evaluated characteristic differences in body height, body weight (BW), body mass index (BMI) and body surface area (BSA) between patients with and without musculoskeletal pain following the discontinuation of IM. These data were analyzed by the Mann-Whitney *U* test, Fisher's exact test and the Log-rank test using Graph PAD Prism 6 (GraphPad Software, San Diego, CA).

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Table 1
Questionnaire of musculoskeletal pain following discontinuation of tyrosine kinase inhibitors in patients with chronic myeloid leukemia.

1. Select the discontinued tyrosine kinase inhibitor below:
☐ Glivec ☐ Tasigna ☐ Sprycel
2. While you were taking the drug selected in Question 1, did you experience any muscle or joint pain? If yes, please select the degree of such pain.
Specific site: ( )
1. Pain not limiting exercise or lifestyle,
2. Pain not causing problems in daily lifestyle but impairing exercise, activities, etc.,
3. Pain limiting daily lifestyle
3. After discontinuation of the drug selected in Question 1, did you experience any muscle or joint pain? If yes, please select the degree of such pain.
Specific site: ( )
Time between discontinuation and the appearance of symptoms: ( )
1. Pain not limiting exercise or lifestyle,
2. Pain not causing problems in daily lifestyle but impairing exercise, activities, etc.,
3. Pain limiting daily lifestyle
4. If, in Question 3, you answered that you experienced physical changes after discontinuation of the drug, for how long did those symptoms persist? Furthermore, was any medication used to treat the symptoms?
Symptom/s that appeared ( )
Duration ( )
Treatment ( )
5. If administration of a tyrosine kinase inhibitor was restarted after discontinuation, did your symptoms change (improve/worsen) after restarting the drug?
☐ No change
☐ Improvement
☐ Exacerbation/new appearance
( )

3. Results

Twenty-four patients were included in this study (16 men, eight women; median age 62 years [range: 37–84 years]). Twenty patients had low, and four had intermediate, Sokal categories. None of the patients had been treated with TKIs other than IM. The median duration of IM therapy was 91.5 months (range: 51–138 months) and the median daily dose was 400 mg (range: 200–400 mg). The time to achieve DMR and the duration of DMR were 36 months (range: 11–84 months) and 50.5 months (range: 31–97 months), respectively.

Seven of the 24 patients developed musculoskeletal pain after discontinuing IM. The median time taken to develop symptoms was 2 weeks (range: 2–4 weeks) and the main locations of pain were the fingers and wrists, although one patient experienced whole body pain. Three patients experienced Grade 3 symptoms on the CTCAE (version 4.0) classification, two of whom were treated with non-steroidal anti-inflammatory drugs (NSAIDs). Symptoms were resolved in six patients after a median duration of 5 months (range: 3–18 months), although symptoms persisted in one patient. We did not observe any abnormality in terms of electrolytes, or CPK/CRP concentrations in any of our patients. Five patients with musculoskeletal pain after discontinuing IM also experienced gastrocnemius pain while they were on IM therapy. Of these, four patients experienced Grade 1–2 symptoms, although the gastrocnemius pain stopped after the discontinuation of IM.

Differences in clinical factors and body characteristics when compared between patients with and without musculoskeletal pain after ceasing IM are shown in Table 2. Body height did not differ between the two groups, however those with symptoms had a significantly lower BW and BMI than those without symptoms ($p = 0.013$, $p = 0.028$, respectively). Furthermore, BSA tended to be lower in those with symptoms; however, this difference was not statistically significant ($p = 0.072$). Clinical factors including sex, age, Sokal category, history of interferon-α, daily IM dose, duration of IM therapy, time to achieve DMR, and the duration of DMR were not significantly different. Finally, the persistence of $MR^{3.0}$ tended to be higher in those with symptoms ($p = 0.077$).

4. Discussion

The main goal of CML therapeutic strategies is the safe discontinuation of TKIs; however withdrawal syndrome is a noteworthy phenomenon after TKI cessation. Although approximately 30% of patients who cease IM reportedly proceed to develop musculoskeletal pain or pruritus [2–5], it is not yet known which factors can predict musculoskeletal pain after the discontinuation of TKIs.

In current study, we focused upon patient physical size parameters such as BW, BMI and BSA. The International Randomized Study of Interferon Versus STI571 (IRIS) study also identified weak correlations between steady-state trough levels of IM and both BW and BSA [6]. Breccia et al. further showed that patients with higher BMIs (25–40 kg/m^2) took significantly longer to achieve complete cytogenetic response and major molecular response than those with lower BMIs (< 25 kg/m^2) [7]. In a prospective Japanese multicenter phase II study, patients receiving 300 mg of IM as tolerable daily doses had a lower BW and BSA than those who could tolerate daily doses of 400 mg although mean trough levels did not differ between these groups [8]. Kim et al. further showed that the pharmacokinetic profile of IM in Korean patients was similar in caucasians [9] and these reports suggested that physical size is related to the pharmacokinetics of IM and associated with treatment effects or adverse reactions.

Table 2
Comparison of clinical factors between patients with and without musculoskeletal pain after discontinuing IM.

	Musculoskeletal pain after discontinuing IM		
	Yes (n = 7)	No (n = 17)	p value
Sex	male 3 female 4	male 13 female 4	0.167*
Age (years) median (range)	54 (44–84)	63 (37–81)	0.181**
Sokal category	low 4 intermediate 3	low 16 intermediate 1	0.059*
Prior IFNα	yes 0 no 7	yes 7 no 10	0.065*
Body height (cm) median (range)	157.4 (154.3–168.5)	166.3 (145.0–180.0)	0.253**
Body weight (kg) median (range)	49.9 (45.6–63.4)	59.0 (47.0–82.6)	0.013**
Body mass index (kg/m^2) median (range)	20.14 (17.45–22.33)	22.01 (19.27–27.16)	0.028**
Body surface area (m^2) median (range)	1.48 (1.41–1.72)	1.67 (1.40–1.98)	0.072**
Daily IM dose (mg) median (range)	400 (200–400)	400 (200–400)	0.594**
IM duration (months) median (range)	86 (56–126)	96 (51–138)	0.744**
IM-DMR (months) median (range)	28 (19–44)	38 (11–84)	0.340**
DMR-IM cessation (months) median (range)	56 (36–97)	50 (31–93)	0.890**
$MR^{3.0}$ maintence after IM cessation	yes 7 no 0	yes 12 no 5	0.077***

Abbreviations: IFNα, interferonα; IM, imatinib; DMR, deep molecular response. Statistical analysis was performed with Graph PAD Prism 6 (GraphPad Software, San Diego, CA).
* with Fisher's exact test.
** Mann-Whitney U test.
*** Log-rank test.

In a previous report, it was speculated that withdrawal syndrome after IM cessation was related to a loss of blocking tyrosine kinases, such as c-kit and platelet-derived growth factor receptor (PDGFR) [2]. The inhibition of c-kit and PDGFR by IM reduces and increases the number of osteoclasts and osteoblasts, respectively; thus, long-term IM therapy can exert influence over bone metabolism and leads to an increased bone volume [10]. In the current study, newly developed joint pain, including the fingers and wrist, was observed following IM cessation. Based upon our findings, we thus hypothesize that patients with a lower BW and BMI may be easily affected by blocking tyrosine kinases, such as c-kit and PDGFR, and these factors are linked to withdrawal syndrome following the discontinuation of IM. By carrying our additional research, and collating as much information as possible, it may be possible to identify positive factors with which to predict withdrawal syndrome following TKI cessation.

Disclosure of interest

Kazuma Ohyashiki received research support from Bristol-Myers Squibb KK and Novartis KK, served as a consultant and advisor for Novartis KK, Bristol-Myers Squibb KK and Ariad, and received lecture honoraria from Novartis KK and Bristol-Myers Squibb KK.

Author's contributions

S.K. performed the research; T.T., K.A., S.O., M.G., and K.O. treated the patients; S.K. wrote the paper while T.T. and K.O. supervised the project. All authors contributed to data analysis, drafting, and revision of the manuscript.

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