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Leptin modification in chronic myeloid leukemia patients treated with imatinib: An emerging effect of targeted therapy. ☆

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ABSTRACT

We evaluated serum leptin levels in 9 young chronic myeloid leukemia (CML) patients under imatinib therapy during a long-term follow-up. Body mass index (BMI) and fat mass percentage (%FM) were also measured. Leptin was above the normal range in 8 out of 9 patients. In one case the hormone was below the reference value. All subjects showed a normal BMI, but 3 had a small increase of FM%. One patient recovered the leptin normal value after imatinib suspension. A tendency to leptin normalization in patients switched to an intermittent therapy was also found. This study suggests that imatinib therapy may result in leptin alteration.

1. Introduction

Chronic myelogenous leukemia (CML), a rare disease in children and young people, is a myeloproliferative neoplasm consistently associated with the *BCR-ABL* fusion gene. The oncoprotein *BCR-ABL*, deranges the balance of cell growth and death in normal hematopoietic cells. The *BCR-ABL* tyrosine kinase (TK) inhibitor, imatinib mesylate (IM), is an effective treatment for CML. Although IM inhibits TKs associated with specific diseases, *in vivo* inhibition of PDGF receptor and c-kit may also occur and may have clinical consequences. IM is well tolerated and molecular remission can be achieved in children and adults. However, altered bone and mineral metabolism [1,2] and severe oligozoospermia [3] in patients taking IM before puberty, and reduction of testosterone and gynecomastia [4], thyreopathy [5] and other endocrinological disorders in a proportion of adult patients has been reported [6].

Leptin, synthesized in adipocytes, is a regulator of fat metabolism and reproduction [7]. The levels of leptin correlate with body fat mass and show a wide variation in individuals. In the bone marrow microenvironment, the leptin secreting adipocytes occupy a significant part [8]. Leptin stimulates hematopoietic stem cells *in vitro*, regulates differentiation within the myeloid and erythroid cell lineage, and is involved in the growth of hematopoietic malignancies [9]. An increase of leptin in IM treated CML adult patients in molecular remission has recently been observed [10]. Here we evaluated the serum leptin concentrations in young CML patients during IM assumption. Our data indicate that, regardless of BMI and percentage of fat mass (FM), long term IM treatment may induce modification of leptin secretion.

2. Subjects and methods

2.1. Patients

Nine patients with CML, under IM, referred to our center for an endocrinological workup, were studied (5 male and 4 female; mean age 17.06 ± 5.5 years). Weight and height were measured and the body mass index (BMI) was calculated as weight in kg divided by the square of height in meters. Follow-up included physical examination, complete blood counts, leptin serum levels and FM% determination. IM was administered orally 400 mg daily. Cytogenetic and molecular responses were assessed periodically. Complete cytogenetic, hematological, and molecular remission (MMolR, BCR-ABL/ABL $< 0.05\%$) was attained and persisted during follow-up, except for a male patient (case 2) who stopped IM after 3.4 years because of a cytogenetic relapse, and underwent stem cell transplantation (SCT). During the study 3 patients (cases 1, 5 and 6) in major molecular response were scheduled to receive an intermittent therapy, consisting in 400 mg daily of IM taken three

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Table 1
Leptin levels, BMI and fat mass during follow-up.

Cases	Sex	Age (yr)	IM administration	Months on IM	Leptin (ng/ml)[a]	BMI (kg/m^2)	FM (%)
1	M	14.0	daily	29	7.9	19.23	17.6
		16.6	daily	59	7.8	18.51	n.a.
		17.6	[b]	71	2.0	18.50	15.6
		18.5	[b]	82	2.1	n.a.	n.a.
2	M	11.3	daily	27	8.5	21.62	n.a.
		12.6	daily	42	16.8	22.5	29.4
		13.2	[c]	—	5.6	18.75	n.a.
3	M	14.8	daily	15	8.5	n.a.	n.a.
		17.9	daily	52	10.1	24.26	22.8
		19.7	daily	74	10.6	22.51	19.3
4	M	22.2	daily	26	39.4	24.0	n.a.
		22.8	daily	32	44.3	n.a.	n.a.
		23.2	daily	38	33.5	24.0	12.4
5	M	15.10	daily	46	< 1	18.57	9.2
		16.5	daily	53	1.2	20	n.a.
		17.4	daily	64	2.2	n.a.	10.7
		18.3	[b]	75	2.1	21.42	11.3
		19.3	[b]	87	2.0	20.52	n.a.
6	F	14.0	daily	48	39.9	19.36	27.4
		15.0	[b]	60	15.6	19.11	n.a.
		15.11	[b]	71	19.3	19.62	32.0
		16.10	[b]	82	20	19.10	32.4
7	F	29.4	daily	6	14.1	23.40	n.a
		31.5	daily	31	13.5	n.a.	34.1
		33.0	daily	50	14.7	24.11	33.7
8	F	14.4	daily	1	32.2	21.48	n.a.
		15.0	daily	9	24.1	n.a.	n.a.
		16.3	daily	24	24.1	22.9	41.0
9	F	18.4	daily	49	15.7	n.a.	n.a.
		19.2	daily	59	13.0	19.85	23.8
		20.11	daily	80	13.7	19.48	23.8

IM: imatinib

[a] normal leptin values: for males 2.0–5.6 ng/ml; for females 3.6–11.1 ng/ml; n.a.: not available
[b] Start of intermittent treatment with IM (3 weeks on and 1 week off per month)
[c] IM discontinuation; FM: body fat mass.

weeks on and one week off every month. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

2.2. Leptin assay

Leptin concentrations were measured using an ELISA kit (human leptin ELISA, Millipore, St. Charles, Mo., USA). The intra- and inter-assay coefficient of variation was 2.6–4.6% and 2.6–6.2%, respectively. Serum leptin concentration was expressed in ng/ml.

2.3. FM evaluation

FM was measured by dual energy X-ray absorptiometry (DEXA) (Hologic Inc., Bedford, MA, USA, QDR 4500W, S/N 47168) by one single experienced technician. Specific delimiters for regional analysis were determined by a standard software (Hologic Inc., QDR 4500W S/N 47168 VER. 11.2). Total body fat mass was expressed in percentage.

3. Results

Table 1 shows the demographic, anthropometric, serum leptin and FM characteristics of the patients during follow-up.

Leptin concentrations were outside the reference values in all patients. In particular, leptin was higher than normal in 8 patients and lower in one (case 5). All the subjects were within the normal BMI range (18.5–24.26 kg/m^2). The FM% was higher than normal in 3 cases. However, on the whole, no apparent relationship was found between the FM% and leptin levels. The patient who interrupted IM after 3.4 years of assumption (case 2) recovered the leptin normal value after drug discontinuation. The three patients who started the IM intermittent treatment (cases 1, 5, and 6), showed a trend toward an improvement of leptin values.

4. Discussion

We determined whether the long-term IM therapy induces leptin modification in young patients treated for CML.

Among the patients under IM in our series, 8 out of 9 had levels of leptin higher than the highest reference range while in one it was lower. In agreement with the reported lack of association between anthropometric measures, including BMI, and CML, [11] all our patients had a normal BMI, indicating that the variation of leptin was not ascribable to an excess of body weight. However, being BMI an inaccurate measure of fatness, we measured the FM% by DEXA. 3 subjects had a FM% higher than normal. In these cases, we cannot rule out an influence of FM excess on leptin values. In the remaining patients, the FM% was within the normal range, suggesting that the modification of leptin may be associated with IM use. As a matter of fact, the highest leptin concentration was measured in a patient with FM% in the lower normal limit.

These results are in line with previous findings [10] showing that, under IM, all CML patients in molecular remission had a significant increase in leptin compared to baseline. A possible causal relationship between IM intake and leptin modification is further reinforced by the results obtained here after IM withdrawal. Infact, one patient who stopped IM and underwent SCT, recovered the leptin normal value. Furthermore, three patients showed a trend toward a normalization of leptin when scheduled to intermittent IM therapy.

An interaction between IM and leptin is made plausible by the sharing of some intracellular signaling pathways and by the interplay with common hematopoietic growth factors. Noteworthy, IM modulates the activity of MEK/MAPK, STAT and other intracellular signals [12] and leptin regulates, and is reciprocally regulated, by the same pathways[13]. Moreover, previous clinical data showed that IM may cause long-term endocrine and metabolic side-effects [1–6]. The receptor for leptin is expressed in hematopoietic stem/progenitor cells. In bone marrow, leptin is secreted from local adipocytes, which occupy most of the marrow cavity in humans, and stimulates myeloid and erythroid development. Therefore, leptin and leptin receptors might play an important role in the control of the expansion and differentiation of primitive hematopoietic cells through paracrine interaction in the bone marrow [8,14,15]. The fat cell content of the bone marrow may thus reflect the requirement for leptin in hematopoietic development. Leptin receptors are also expressed in leukemic cells from patients affected by CML, acute myeloblastic leukemia and acute lymphoblastic leukemia. Particularly, in CML higher expression of leptin receptors has been observed during blast crisis than in the chronic phase [16]. Moreover, leptin alone and in combination with other cytokines, shows anti-apoptotic and proliferative effects on leukemia cells, suggesting that leptin may play an active role in the pathophysiology of leukemia [16]. All together, these data reinforce the view that IM may influence either directly or indirectly leptin.

This study has some limitations. First, the sample size allows only a partial conclusion, although patients were monitored for a long period and CML is a rare disease in young people. The lack of leptin measurements before IM is a further limitation, although the out of range values found during the follow-up could be an attracting starting point for future research. Finally, the time intervals in the monitoring of the patients were irregular.

In conclusion, the knowledge of the side effects of TKs inhibitors is increasing. Nonetheless, the patients chronically exposed to targeted therapies need investigations on long-term side effects of these drugs. The identification of specific hormonal profiles that correlate with tumor progression or with the success of the therapy may represent an important step in evaluating potential target therapy. These data will contribute to a better understanding of the mechanism of TK inhibitors action and of their safety profile.

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