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Study on Serum Status of Insulin like Growth Factor-1 (IGF-1) Levels in CML Patients before and after Imitanib Therapy

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Abstract **Original Research Article**

CML is a common haematological malignancy characterized by the BCR-ABL fusion gene and treated by the tyrosine kinase inhibitor imatinib which has also been shown to inhibit other tyrosine kinases involved in multiple endocrine functions. IGF-1 as a part of Growth hormone IGF-1 axis is involved in bone growth and haematopoiesis. IGF-1 deregulation has been shown to be associated with multiple cancers and CML. Further it is postulated to have a role in blast crisis transformation of CML and its metabolism may be affected by imatinib. All these intriguing interactions and lack of studies on status of serum IGF-1 in CML patients and the effect of imatinib therapy on them inspires this study. The study was designed to prospectively study serum IGF-1 levels at baseline and at 6 months of imatinib treatment in 30 newly diagnosed BCR-ABL positive CML patients. IGF-1 levels were measured with commercial ELISA kit. Of the 30 CML patients (17M & 13F), 2 patients presented in accelerated phase and 26 achieved haematological remission by 6 months. There was no significant difference in serum IGF-1 levels in patients (186.8±42.0 ng/mL) and controls (173.0±53.1 ng/mL). Mean baseline levels in 4 patients not achieving hematological remission by 6 months were 203.6±28.4 ng/mL as compared to 184.3±43.5 ng/mL in the rest achieving hematological remission. Serum IGF-1 levels decreased significantly with age in both controls ($r^2 = 0.309$, $p<0.001$) and patients ($r^2 = 0.314$, $p<0.001$). Serum IGF-1 levels decreased significantly after 6 months of imatinib therapy in patients in hematological remission (104.9±43.8 ng/mL vs. 184.3±43.6 ng/mL, $p <0.001$). Significantly decreased serum IGF-1 levels after 6 months of imatinib therapy reflect the GH deficiency induced by imatinib therapy in the adult CML patients. Further longitudinal studies in larger number of patients are required to assess the clinical significance of GH and IGF-1 deficiency in adult CML patients on imatinib therapy and speculated protective effect of IGF-1 from blast crisis development.

Keywords: CML, IGF-1, Imatinib.

INTRODUCTION

CML: Chronic myelogenous leukemia is a myeloproliferative disorder in which hematopoietic cells contain the fusion gene BCR-ABL, which encodes a constitutively active tyrosine kinase responsible for the initiation and maintenance of the chronic phase of CML [1, 2]. The natural history of the chronic phase (CP) of the disease is to undergo clonal evolution into an accelerated phase (AP) and/or a rapidly progressive phase (blast crisis, BC) resembling acute leukemia [3]. Imatinib mesylate, the drug used to treat CML acts by competitive inhibition at the ATP binding site of the ABL kinase which leads to inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction and thus apoptosis of the malignant cells [4,5]. The goal of imatinib therapy is to decrease the cells bearing the t (9; 22) translocation (leukemic cells) to the lowest levels possible (BCR-ABL/ABL expression ratio <0.05% by 18 months of therapy), under which conditions normal (polyclonal) haematopoiesis is restored [1]. Besides BCR–ABL imatinib mesylate has been shown to inhibit the platelet derived growth factor receptor-α (PDGFR-α), PDGFR-β, c-Fms, Arg and c-kit (stem cell factor receptor) tyrosine kinases leading to side effects and endocrine disturbances. Effects of imatinib on multiple endocrine hormones are being recognized and may affect quality of life in the CML patients and cause compliance issues [6].

IGF-1: IGF-I is mainly secreted by liver as a result of stimulation by GH. IGF-I/GH axis is required for advancing maximal growth postnatally [7]. In adults IGF-I levels range between 150-350 ng/ml. Factors that are known to cause variation in the levels of growth hormone and IGF-I in blood include an individual's genetic makeup, exercise status, stress level, nutrition, disease state, race, estrogen status and xenobiotic intake [8, 9]. Levels of circulating IGF-I change substantially with age; they increase slowly from birth to puberty, surge at puberty and decline with age thereafter. Mean serum IGF-I levels are low in GH-deficient adults, and very low IGF-I levels can indicate GH deficiency. IGF-1 acts by increasing DNA synthesis and by stimulating the expression of cyclin D1, which accelerates progression of cell cycle from G1 to S phase. IGF-I is a strong mitogen for a wide variety of cancer cell lines including sarcoma, leukemia and a number of solid tumors[10,11]. Elevated IGF-1 expression or levels have been demonstrated in multiple cancers. GH and IGF-I stimulate cartilage growth and lengthen bones causing statural growth. By controlling the size of the bones in the growing animal, GH and IGF-I therefore indirectly control the volume of bone marrow and thus the production of hematopoietic cells. Recent evidence shows that IGF-I differs from insulin in that, at physiological concentrations, it also plays a direct and significant role in regulating haematopoiesis and immune function[11,12] Majka *et al.* concluded that normal human CD34(+) cells and hematopoietic precursors secrete numerous regulatory molecules including IGF-1. Bone marrow stromal cells also release IGF-I[13]. Endogenously secreted IGF-1 has the potential to regulate adhesion, proliferation and apoptosis of hematopoietic cells and to regulate activity of accessory cells [14, 15]. Involvement of IGF-1 in normal and malignant hematopoiesis has been documented [16]. Shimon *et al*. found that nearly all the different hematopoietic cells, either normal or neoplastic; express IGF-1 receptors [17].

IGF-1 in CML: Hizuka *et al*. describe the presence of specific IGF-I receptors on a human CML cell line (K-562 cells) [18]. Shi *et al*. showed that IGF-I receptor is also universally expressed in four CML cell lines. IGF-IR was expressed in only 30% and 25% of chronic phase accelerated phase patients, respectively, but its frequency of expression increased to 73% of blast crisis patients. Inhibition of IGF-I receptor decreased the viability and proliferation of CML cell lines and abrogated their growth in soft agar [19]. Kim *et al*. demonstrated that the human chronic myelogenous leukemia cell K562, highly expresses IGF-I, IGF-II, IGF-I receptor, and IGF-induced cellular proliferation is mediated by IGF-I receptor [20]. However Zadik *et al*. observed that in 3 CML patients in remission a granulocyte-macrophage colony forming assay did not reveal stimulation of peripheral blood blast colony formation by GH or IGF-I [21]. Though multiple in-vitro studies have described expression of IGF receptor on CML cells and BCR-ABL has been described to induce IGF-1 autocrine signalling, others did not reveal any role of IGF-1. Further conditions with increased IGF-1 levels like acromegaly and GH therapy have been associated with leukemias. Leukemia development in the course of GH therapy was first reported from Japan in 1987. Many cases have been reported associated with the development of leukemia due to GH therapy [22, 23].

Imatinib and IGF-1: Tyrosine kinase (TK) is essential in the hypophysis for the secretion and action of growth hormone. Chronic fatigue a common and unexplained side effect of imatinib mesylate is also the feature of GH deficiency [21]. Kebapcilar *et al.* demonstrated that a large number of the adult CML patients (17) on imatinib mesylate therapy had GH deficiency and lower IGF-1 levels [24]. Several other case reports have documented growth delay of unknown mechanism and decreased IGF-1 levels in children with CML treated with imatinib [25-27]. However Oliveira *et al*. showed that subjects with CML do not have depressed GH production [28]. Pastural *et al.* suggested a relationship between high levels of IGF and blastic crisis in CML patients. From that perspective, it has also been speculated that the amelioration of GH and IGF levels induced by imatinib mesylate may protect from blastic transformation [29]. There is a lack of studies on status of serum IGF-1 in adult CML patients.

METHODOLOGY

The study was a prospective, nonrandomized, observational study conducted on 30 newly diagnosed patients of CML (17 males and 13 females) in chronic phase. Thirty age and sex matched healthy controls (17 males and 13 females) were also taken. Patients were recruited from the Haematology clinic in Post Graduate Institute of Medical Sciences, Rohtak, and Haryana after taking informed consent. Ethical approval was obtained from the institutional board of studies. Diagnosis was made by history, clinical examination, total and differential leukocyte count, and bone marrow examination and further confirmed by real-time PCR for BCR-ABL fusion transcript. Exclusion criteria: patients with other acute or chronic co-morbidities like liver and kidney diseases, endocrine disorders, other malignancies, CML-blast crisis, chronic infections like tuberculosis, etc. and those taking any other medication besides imatinib and haematinics (folic acid, vitamin B12, vitamin B6, iron, etc.) were excluded. Imatinib therapy was given initially in a dosage of 400 mg/day and increased to 600 mg/day or to 800 mg/day (400 mg every 12 h), if required and tolerated [2, 4]. Haematological remission criteria were used for evaluation of response and were defined as total leukocyte count<$10X10^9$/l, platelet count < $450X10^9$/l, no immature myeloid cells in the blood, disappearance of all signs and symptoms related to leukaemia

(including palpable splenomegaly) lasting for at least 4 weeks [4, 5]. Serum IGF-1 levels, routine biochemical investigations and other relevant investigations were done at the time of diagnosis (baseline) and in controls. IGF-1 levels and other tests were repeated at 6 months or first complete remission (whichever is earlier) in CML patients.

IGF-1 estimation: For biochemical testing fasting early morning venous blood sample was taken in a plain red capped evacuated blood collection tube under all aseptic precautions. Samples were processed within one hour of collection. Serum was separated by centrifugation at 3000 rpm X 10 minutes after clotting. Separated serum was stored at -20^{0}C until analysis. Serum IGF-1 levels was estimated by a commercial Enzyme Linked Immunosorbent Assay kit for human IGF-1 from DRG.

Statistical analysis

The data were compiled and subject to statistical analysis using SPSS v20. Baseline and post-therapy values were compared using Wilcoxon signed rank test. Comparison of data between groups was done using Mann Whitney Test for quantitative data and Chi-square test for qualitative data. Correlations and regression between groups were analyzed using suitable models. Spearman's correlation coefficient (r) formula was used to assess correlations.

OBSERVATIONS

Patient characteristics: During the study 33 patients enrolled of which 3 were excluded due to diagnosis of blast crisis. Mean age at diagnosis was 39.5±12.7 years and was comparable with mean age of controls (37.2±11.1 years). Median duration of history of presenting illness was 6 weeks in CML patients. 10% patients were asymptomatic and diagnosed incidentally on routine lab examination. 2 (6.7%) patients presented with accelerated phase of disease (blast count 10-20%). 26 patients (87.7%) achieved remission at 6 month of imatinib therapy while 4 (13.3%) patients were not in haematological remission. None of the patients had any significant side effect form imatinib therapy to warrant dose reduction or discontinuation. Clinical and hematological features at diagnosis are summarized in table 1.

Table-1: Clinical and hematological features at diagnosis in CML patients

	CML (n=30)
Median Duration	6 weeks (asymptomatic – 3)
Fever	21 (70%)
Weakness	27 (90%)
H/o Bleeding	3 (10%)
Spleenomegaly	22 (73.3%)
Hepatomegaly	18 (60%)
LAP	1 (3.3%)
Median Hb	8.5 g/dL
Median TLC	75,000 / cu.mm
Median Platelet count	3,00,000 / cu.mm
Median Blast%	5.5 %

IGF-1 status: There was no significant difference in serum IGF-1 levels in patients (186.8±42.0 ng/mL) and controls 173.0±53.1 ng/mL, figure 1). Mean levels in the 2 patients presenting in accelerated phase was 233 ng/mL as compared to 183.5±39.1 ng/mL in rest of the patients in chronic phase of the disease. The difference was not statistically significant (Figure 1). Mean baseline levels in the 4 patients who were not on haematological remission at 6 months were 203.6±28.4 ng/mL as compared to 184.3±43.5 ng/mL in the remaining 26 patients who were in haematological remission. The difference was not statistically significant. Serum IGF-1 levels decreased significantly with age in both controls (r^2 = 0.309, p<0.001, figure 2) and patients (r^2 = 0.314, p<0.001, figure 3). Serum IGF-1 levels decreased significantly after 6 months of imatinib therapy in patients in haematological remission (104.9±43.8 ng/mL vs. 184.3±43.6 ng/mL, p <0.001, table 2 & figure 4). Serum IGF-1 levels decreased to 108.6±35.0 ng/mL after 6 months of imatinib therapy from initial levels of 203.6±28.4 ng/mL in patients not in haematological remission but the difference was not statistically significant probably due to small number of such patients (table 2 and figure 4).

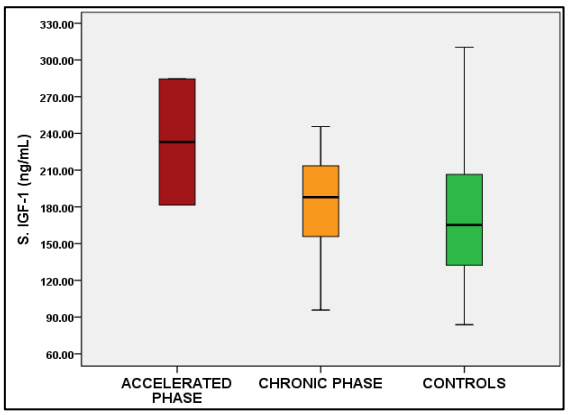

Fig-1: Comparison of S. IGF-1 in CML patients with controls

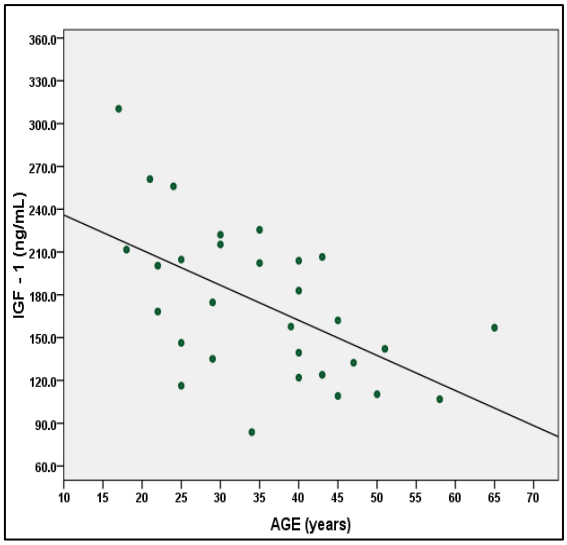

Fig-2: Correlation of S. IGF-1 and age in controls

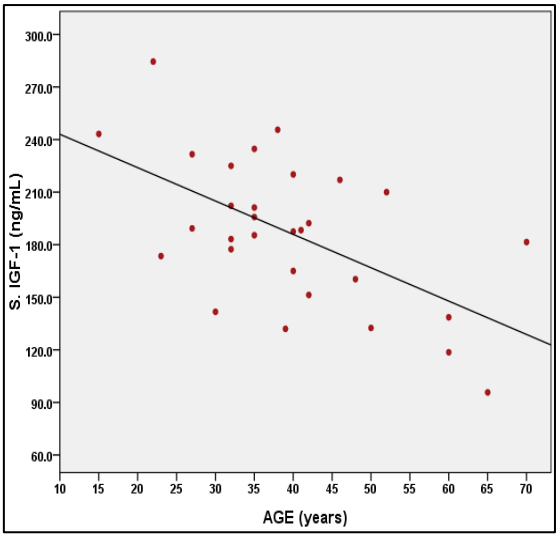

Fig-3: Correlation of S. IGF-1 and age in CML patients

Table-2: Comparison of S.IGF-1 levels before and after therapy in CML patients

Pre and Post therapy in comparison in patients achieving haematological remission at 6 months			
S. IGF-1 (ng/mL)	**BEFORE THERAPY (n=26)**	**AFTER THERAPY (n=26)**	**p value**
Mean	184.3 ± 43.6	104.9 ± 43.8	<0.001
Pre and Post therapy in comparison in patients not in haematological remission at 6 months			
S. IGF-1 (ng/mL)	**BEFORE THERAPY (n=4)**	**AFTER THERAPY (n=4)**	**p value**
Mean	203.6 ± 28.4	108.6 ± 35.0	0.068

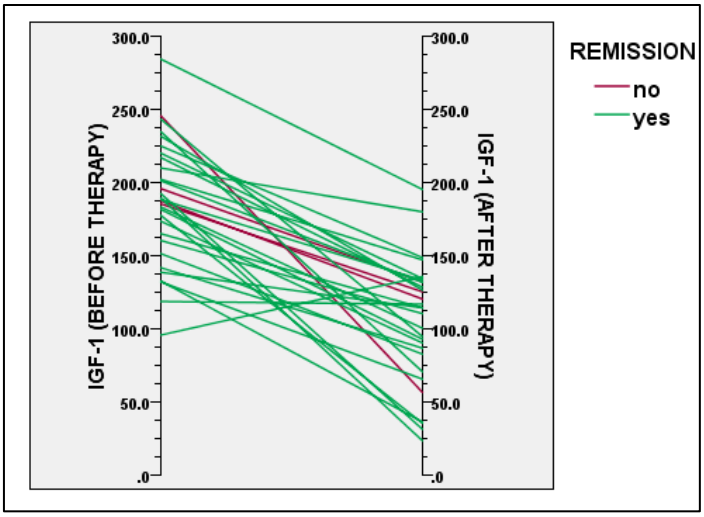

Fig-4: Comparison of S. IGF-1 before and after therapy in CML patients

DISCUSSION

Mean age at diagnosis was 39.5±12.7 years with 17 out of 30 patients being male. In general, the male predominance has been estimated to be 1.3-1.4:1. Though the incidence of CML has been known to increase logarithmically with age, Dikshit *et al*. noted the peak age in younger population in hospital based data than the peak age of 55–74 years noted in population based studies[30]. Median duration of history of presenting illness was 6 weeks. Three out of 30 patients were asymptomatic and diagnosed incidentally on routine lab examination. Detection of CML as incidental finding on routine blood examination is known to occur in up to 10% of cases [30]. The total leukocyte count is always elevated at the time of diagnosis and has been reported to be nearly always greater than 25,000/cu.mm. More than 50% of patients have been reported to have TLC > 1, 00,000/cu.mm at diagnosis in literature. The

mean blast cell prevalence has been reported to be approximately 3% but can range from 0 to 10% [30]. 26 patients (87.7%) achieved remission at 6 month of imatinib therapy while 4 (13.3%) patients were not in hematological remission. The hematologic remission rate of patients treated with imatinib has been reported to be 95%. Because early, quiescent Ph-chromosome–positive cells (CD34+Lin–) are insensitive to imatinib in vitro, at present it is advisable to maintain treatment indefinitely until the criteria for cessation, if any, can be established in clinical trials[1]. This further makes assessment of endocrine effects of imatinib clinically significant.

IGF-1: Serum IGF-1 levels decreased significantly with age in both controls (r^2 = 0.309, $p<0.001$, figure 2) and patients (r^2 = 0.314, $p<0.001$, figure 2&3). Serum IGF-1 concentrations have been reported to decline with age in both males and females after the age of 18 while levels were found to be similar in adult male and females[11]. The present study did not find any significant difference in IGF-1 levels in CML patients as compared to controls and no association of IGF-1 levels with known prognostic factors (figure1). Many authors demonstrated that IGF-1 in physiological concentrations promotes myelopoeisis, erythropoiesis and proliferation of T-cells [8, 10, 12-14, 17, 31]. Majka *et al*. concluded that normal human CD34 (+) cells and hematopoietic precursors secrete numerous regulatory molecules including IGF-1. Bone marrow stromal cells also release IGF-I and IGF binding proteins [13]. IGF-1 receptor has been described to be expressed on CML cell lines. Shi *et al*. demonstrated that IGF-IR is universally expressed in four CML cell lines. IGF-IR was expressed in only 30% and 25% of chronic phase (CP) and accelerated phase (AP) patients, respectively, but its frequency of expression increased to 73% of blast crisis (BC) patients. Inhibition of IGF-IR decreased the viability and proliferation of CML cell lines and abrogated their growth in soft agar [19]. Kim *et al*. demonstrated that the human CML cell K562, highly expresses IGF-I, IGF-II, IGF-IR, and IGF-induced cellular proliferation is mediated by IGF-IR. IGF-1-blocking antibody was also used to demonstrate the importance of autocrine IGF-1 signalling in CML-BC cell line viability [20]. Multiple in-vitro studies have described expression of IGF receptor on CML cells and BCR-ABL has been described to induce IGF-1 autocrine signalling. Inhibition of IGF-1 receptor on CML cells led to their apoptosis [29]. Alterations in such autocrine and paracrine signalling may or may not affect the systemic blood levels. The present study did not find any significant alterations in IGF-1 levels in CML patients at diagnosis when compared to controls. IGF-1 signalling may facilitate transformation to blast crisis. Lakshmikuttyamma *et al*. observed overexpression of IGF-1 in CML-blast crisis. In their study in 8 out of 11 matched CML patient biopsies, the IGF-1 expression was elevated in blast crisis. Thus they suggested that aberrant IGF-1 signaling is an important event in blast crisis transformation and it provides a mechanism to explain the activity of IGF-1 receptor and Hemopoietic cell kinase (Hck) inhibitors in blocking CML-BC phenotypes [32]. Higher mean levels in the 2 of 30 patients presenting in accelerated phase and higher mean levels in the 4 of 30 patients who did not achieve haematological remission at 6 months in the present study may be indicative of involvement of IGF-1 in transformation to accelerated phase and blast crisis, but larger sample size study is needed to produce statistically significant results. Pastural *et al*. demonstrated decreased expression of RIZ1, an inhibitor of IGF-1 expression. RIZ1 is a histone methyltransferase whose expression and activity are reduced in many cancers. Forced RIZ1 expression in model CML blast crisis cell lines decreased proliferation, increases apoptosis and enhances differentiation possibly by inhibiting IGF-1 expression. IGF-1-blocking antibody was also used to demonstrate the importance of autocrine IGF-1 signaling in CML-Blast crisis cell line viability [29].

Imatinib and IGF-1: Serum IGF-1 levels decreased significantly after 6 months of imatinib therapy in patients in haematological remission (table 2 & figure 4). Serum IGF-1 levels also decreased after 6 months of imatinib therapy from initial levels in patients not in haematological remission but the difference was not statistically significant probably due to small number of such patients (table 2 & figure 4). These may reflect the GH deficiency (GHD) induced by imatinib therapy in the adult CML patients. Kebapcilar *et al*. also demonstrated that a large number of the adult CML patients (17) on imatinib mesylate therapy had GH deficiency. They found lower IGF-1 and IGFBP-3 levels in CML patients taking imatinib mesylate. 58-70 % patients on imatinib had low IGF-1 levels indicative of GH deficiency. Nine subjects (52%) had both severe GHD based on glucagon stimulation test (GST) response and IGF-I levels [24]. Several other case reports have documented growth delay of unknown mechanism in children with CML treated with imatinib. Hobernicht *et al*. reported a seven-year-old identical twin with CML who developed significant growth delay, as compared to her twin, during four years of TKI therapy. IGF-1 levels were decreased in the patient and levels normalized by GH supplementation [26]. Schmid *et al*. reported longitudinal growth retardation in a pre-pubertal girl with CML on long-term treatment with imatinib. While at diagnosis her height was equivalent to the 74th percentile it fell to the 9th percentile after three years of treatment. Diagnostics showed partial GH deficiency (IGF1: 43 ng/mL and 60 ng/mL at the age of seven years and eight years, respectively: normal values: 64-345 ng/mL). Her two heterozygous triplet siblings showed normal hematologic parameters and their growth followed the 82nd and 55th percentiles, respectively [27]. However Oliveira *et al*. showed that adult subjects with CML do not have depressed GH production [28].

Rastogi *et al*. reported that growth in children with CML appears to be adversely impacted by imatinib therapy, but as BMI and IGF-1/IGFBP-3 were maintained during treatment, they suggested a direct effect of imatinib on the growth plate [33]. Tyrosine kinase (TK) is essential in the hypophysis for the secretion and action of growth hormone both centrally and within the peripheral targets. GH releasing hormone is released from the hypothalamus and binds to the GH receptors on somatotropes in the anterior pituitary. Signal transduction by these somatotropes varies depending on the activating signal but is ultimately mediated by activated adenylate cyclase/cAMP pathways, mobilization of intracellular calcium, TKs, and nitric oxide/cGMP. Within the peripheral targets, the initial signalling event in GH is activation of the TK JAK2 that in turn phosphorylates tyrosines within JAK2 and GHR. This mediates further downstream signaling and initiates IGF-1 gene transcription in the liver and other target tissues. The effects of IGF receptor activation are mediated by additional TK activation that then activate specific cellular pathways and exert growth-promoting actions via GH receptors on the epiphysis itself [11, 24]. The findings of significantly decreased IGF-1 levels in adult CML patients after 6 months of imatinib therapy in the present study are suggestive of GH deficiency. As a relationship between high levels of IGF and blast crisis in CML patients has been described in literature, it has been speculated that the amelioration of GH and IGF levels induced by imatinib mesylate may protect from blastic transformation [29]. Thus further longitudinal studies in larger number of patients are required to assess the clinical significance of GH and IGF-1 deficiency in adult CML patients on imatinib therapy and speculated protective effect of IGF-1 from blast crisis development.

CONCLUSIONS

Serum IGF-1 levels were found similar in cases and controls. Significantly decreased serum IGF-1 levels after 6 months of imatinib therapy reflect the GH deficiency induced by imatinib therapy in the adult CML patients. Further longitudinal studies in larger number of patients are required to assess the clinical significance of IGF-1 deficiency in adult CML patients on imatinib therapy and speculated protective effect of IGF-1 from blast crisis development. Effect of imatinib on GH-IGF-1 axis also needs to be studied in pediatric cases. The limited data of the current study suggests that Imatinib treatment can be maintained indefinitely if tolerated well and its effect on GH-IGF-1 axis in adults does not has any major clinical implications. But the minor effects of imatinib on general well being and quality of life due to reduced IGF-1 levels (GHD) will need to be evaluated in greater detail as more and more patients continue imatinib as a life-long therapy.

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