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Research Article

Assessment of the effects of Imatinib mesylate (Glivec) therapy on CD4+ T lymphocytes and serum immunoglobulins in a cohort of Nigerian Chronic myeloid leukaemia patients

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Abstract

Objectives: To investigate the effects of Glivec on some aspects of immunity in CML patients.

Patients and Methods: We prospectively assessed some immunological parameters in 50 Nigerian CML patients before and six months into Glivec therapy. FBC, CD4+ T lymphocytes, serum IgG, IgM, and IgA, plasma total proteins, albumin and globulin were assessed at diagnosis and at 6 months of Glivec therapy. CD4+ lymphocyte count was carried out using Class 1 Cyflow Counter. FBC was done using manual method and ALC calculated from total WBC and the differential count of lymphocytes. Serum immunoglobulins were measured using ELISA method. Biuret method was used to measure total protein; while BCG dye binding method was used for serum albumin.

Results: After 6 months of therapy, 70% of subjects were in haematological remission with a significant reduction in the mean CD4+ lymphocyte count and mean serum IgA ($p < 0.000$, respectively). No significant differences were found in the mean IgG and IgM; and between the values of the immunological parameters between those in haematological remission and those that were not in remission.

Conclusions: This study suggests that Imatinib can affect some aspects of the immunity. However, infection is not a major problem in them.

ABBREVIATIONS

CML = Chronic Myeloid Leukaemia; Ig = Immunoglobulin; WBC = White Blood Cell

INTRODUCTION

Chronic myeloid leukaemia (CML) is a malignant clonal disorder of haematopoietic stem cells that results in increases in not only myeloid cells but also erythroid cells and platelets in peripheral blood and marked myeloid hyperplasia in the bone marrow [1]. It was the first human malignancy to be linked to a specific acquired genetic abnormality, Philadelphia chromosome (Ph+), which results from a reciprocal translocation between chromosomes 9 (q34) and 22 (q11) [2], and the first neoplastic disease for which knowledge of the genotype led to a rationally designed therapy [3]. The oncogenic chimeric BCL/ABL gene also evolves from the Ph chromosome.

Imatinib mesylate (Glivec) manufactured and distributed by Novartis Pharmaceuticals, (East Hanover, NJ) was approved on May 10th 2001 by the US Food and Drug Administration for the treatment of CML [4]. It is a selective inhibitor of the bcr/abl tyrosine kinase, which deregulated expression is involved in the pathogenesis of CML. However, recent observations in its use have shown it to also affect non-malignant haemopoietic cells: inhibiting the proliferation, differentiation and maturation of human CD34+ progenitor cells [5]. It affects the differentiation of CD34+ progenitor cells into dendritic cells (DCs), affects the development of DCs and their capacity to induce primary cytotoxic T-cell response in vitro. Studies have also shown that it depresses cytokine production by CD4+ and CD8+ T lymphocytes, thus, suggesting that the effector functions of T lymphocytes may be reduced in the presence of Imatinib [5]. Clinical studies have reported peritoneal tuberculosis and lymphopenia in a CML patient on Glivec who is not exposed to mycobacterial infection and is HIV negative [6]. Recently, we also reported lymphopenia and reduced CD4+ lymphocytes in a small cohort of CML patients [7] and reactivation of latent herpes zoster infection in a gastrointestinal stromal tumour (GIST) patient on IM therapy [8]; suggesting that cell-mediated immunity is also frequently impaired, especially in the advanced stages of the disease in the presence of IM. Santachiara et al [9] reported the development of hypogammaglobulinemia in CML and gastrointestinal stromal tumour patients treated with Imatinib mesylate; while Steegmann et al [10] and Humlova et al [11] also reported reduced serum levels of some immunoglobulins in patients treated with the drug.

In view of current availability of Imatinib mesylate to Nigerians with CML courtesy of Novartis's Glivec International Patient-Assistance Programme (GIPAP: www.maxaid.org) we investigated the effects of IM on some aspects of the cellular and humoral immune system in our patients currently on the drug.

MATERIALS AND METHODS

The work was based on a prospective cohort study. Newly diagnosed CML patients confirmed to be Ph+ and/or bcr/abl positive were recruited after obtaining informed consent. Non-probability sampling method was used to serially recruit 50 patients who are 15 years or older into the study. Each patient was investigated pre-therapy and at six months of Imatinib treatment. Patients suffering from immunosuppressive disorders such as Tuberculosis or HIV/AIDS, or on immunosuppressive drugs for other disorders were excluded. Approval was obtained from the Institution's Ethics and Research Committee.

Complete blood count (PCV, WBC and differentials, and platelet count) were carried out within 6 hours of sample collection using manual methods as described by Dacie and Lewis [12]. CD4+ cells counts were done, using Class 1 Cyflow Counter (Laser Product, Partec Germany) and following the manufacturer procedures. CD4+ cells were counted not later than 12 noon on the day of sample collection.

The serum concentrations of IgG, IgM and IgA were measured using human IgG, IgM and IgA ELISA Kits, respectively, (Immunology Consultants Laboratory, Inc. Portland, USA) following manufacturer's instructions. Total serum proteins concentrations were estimated using Biuret method; while Bromocresol Green dye binding method was used for albumin estimation.

Patients' data were entered into Statistical Package for Social Science (SPSS), version 16, to carry out statistical analyses. For quantitative variables, medians and ranges, means and standard deviations were determined. Paired T-tests were used to compare quantitative variables before and after therapy for normally distributed (non-skewed) data and Wilcoxon matched-pair signed rank test and Student T-test and Mann-Whitney U test were used for two independent groups for non-skewed and skewed data, respectively. Pearson correlation statistics was also computed for two continuous variables as appropriate. The level of significance for all statistical analysis was set at 5%.

RESULTS

Fifty subjects were investigated before commencing Imatinib therapy. Using the Sokal score [13], the majority of our patients, 36/50 or 72%, were in the high risk group; while the rest 14 (28%) were in the intermediate risk group [Table 1]. Patients in chronic phase were placed on standard dose of 400mg daily, while those in accelerated or blastic transformation were on 600mg daily. Their ages ranged between 18 and 86 years (median age = 38.5 years) with 30 (60%) males and 20 (40%) females (M: F = 1.5:1). The majority of the patients were in the 25-39 and 40-59 years age groups (76%) [Table 2]. Fourty-two patients (84%) were already commenced on Hydroxyurea with a median period of six weeks and a range of 20 weeks before enrollment on Glivec therapy; while 8 patients (16%) were not on any form of chemotherapy before we investigated them. Fourty seven patients (94%) were in chronic phase at the time of enrollment, while the remaining three patients (6%) were in accelerated phase. Common risk factor for infection [14] such as diabetes mellitus, smoking, alcoholism, old age, or a combination any of these were found in only 30% of them; while the majority were without any observable risk factors.

Table 3 showed the haematological parameters assessed pretherapy and six months after Glivec therapy. After 6 months of treatment, 70% (35/50) of patients were in haematological remission. The mean ± SD of CD4+ lymphocytes was found to be 1671 ± 982.37 cells/ μL with a range of 5752 cells/ μL (median = 1725 cells/μL) before Imatinib therapy, while after six months of therapy, the value was 1023.98 ± 453.24 cells/ μL with a range of 1785 cells/ μL (median = 947.50 cells/ μL). The difference was significant ($t = 4.96$, $p < 0.000$) [Figure 1]. The pre-therapy CD4+ lymphocytes value correlated positively ($r = 0.607$, $p = 0.000$) with total WBC [Figure 2] and with absolute lymphocytes count ($r = 0.366$, $p = 0.009$). Similarly, the value CD4+ lymphocytes count and ALC obtained after six months of treatment correlated positively ($r = 0.463$, $p = 0.001$) [Figure 3]. However, there a weak correlation between CD4+ lymphocytes and total WBC six months into therapy ($r = 0.279$, $p = 0.049$). We also found a significant difference ($t = -11.05$, $p = 0.000$) in the mean of lymphocyte percentage count pre- (15.08 ± 13.62) and six months into therapy (48.12 ± 18.16) and a significant reduction in absolute neutrophils counts (post-therapy: 4, 040.99 ± 8106.07 and pre-therapy: 75, 322.28 ± 85985.31; $t = 3.823$, $p < 0.000$).

Table 4 showed the values for immunoglobulins and total

Table 1: Risk Categories of Patient using Sokal Score [13].

Risk Category	N (%)
Low Risk (< 0.8)	0 (0%)
Intermediate Risk (0.8 – 1.2)	14 (28%)
High Risk (> 1.2)	**36 (72%)**

Table 2: Patients' demographic characteristic.

Age group (years)	No	%
≤24	7	14
25 – 39	19	38
40 – 59	19	38
≥60	5	10

Table 3: Comparison of haematological parameters of CML patients pretherapy and 6 months into Imatinib therapy.

Parameters	Mean Pre-Therapy	Mean Post-Therapy	t	p value
PCV (%)	29.54	36.00	-4.95	0.000
WBC (/µL)	157586.60	7615.48	6.76	0.000
PLT (/µL)	307090	248090	1.60	0.110
Neut. (/µL)	49.72	44.92	1.42	0.163
Lymph (/µL)	15.08	48.12	-11.05	0.000
ANC (/µL)	75322.28	4040.99	5.83	0.000
ALC (/µL)	16234.07	2557.66	3.82	0.000
ESR (mm/hr)	60.19	30.88	5.37	0.000
CD4+ (/µL)	1671.76	1023.98	4.96	0.000

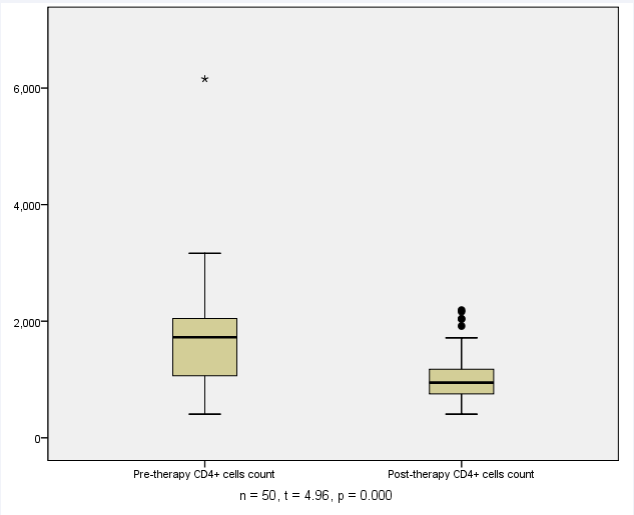

Figure 1 Pre-and post-therapy CD4⁺ cells count in CML patients.

serum proteins assessed pretherapy and six months after Glivec therapy. The difference between the post-therapy mean serum total protein (72.40 ± 8.23mg/dL) and pre-therapy (75.52 ± 9.39mg/dL) values were not significant. Similarly, the difference in the post-therapy and pre-therapy values we obtained for both albumin (35.82 ± 4.52 versus 36.80 ± 4.52) and globulin (36.78 ± 7.53 versus 38.68 ± 8.09) were not significant; though post-therapy values were slightly reduced. Expectedly, total serum protein correlated positively with both albumin and globulin (r = 0.499, p < 0.000; r = 0.858, p < 0.000, respectively). However, unexpectedly, there was no correlation between plasma globulin and the serum immunoglobulins.

The mean pre-therapy serum IgG levels in our subjects was 1984.60 ± 965.43mg /dL, with a range of 3560mg/dL (median = 1708mg/dL). The post-therapy mean value was 2067.72 ± 1209.07mg/dL with a range of 3280.00mg/dL (median = 1405.00mg/dL). We did not find any significant difference between the two values. However, 58% (21/50) of the subjects actually had reduced values from their pre-therapy values 6 months after. Unexpectedly too, 42% (21/50) of them had increased serum IgG levels after 6 months on treatment.

The pre-therapy mean serum IgA levels in our cohort was 236.92 ± 181.35mg /dL with range of 795.00mg/dL (median = 171.00mg/dL); while the post-therapy mean value was 120.62 ± 56.78mg/dL with a range of 214.00mg/dL (median = 114.00mg/

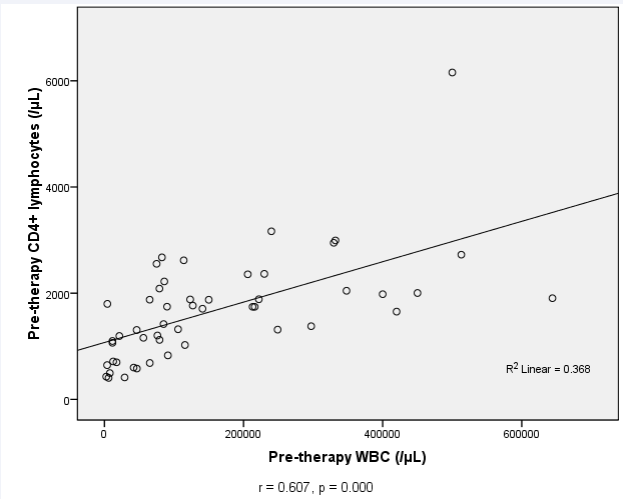

Figure 2 Correlation between CD+ T-lymphocytes and WBC count pre-therapy in CML patients.

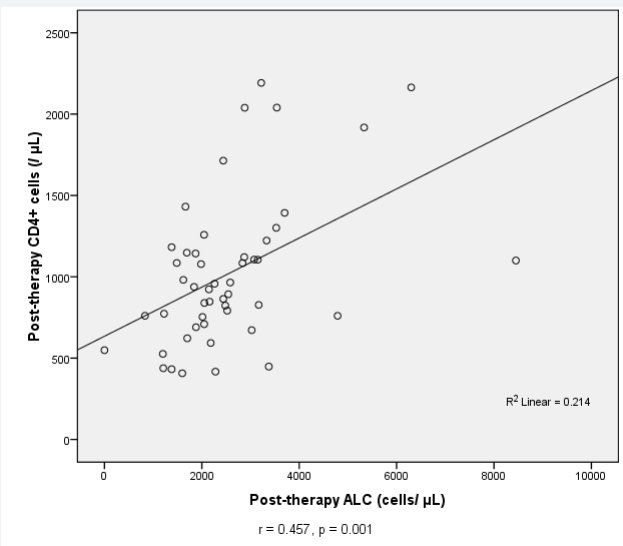

Figure 3 Correlation between CD4⁺ lymphocytes and ALC post-therapy in CML patients.

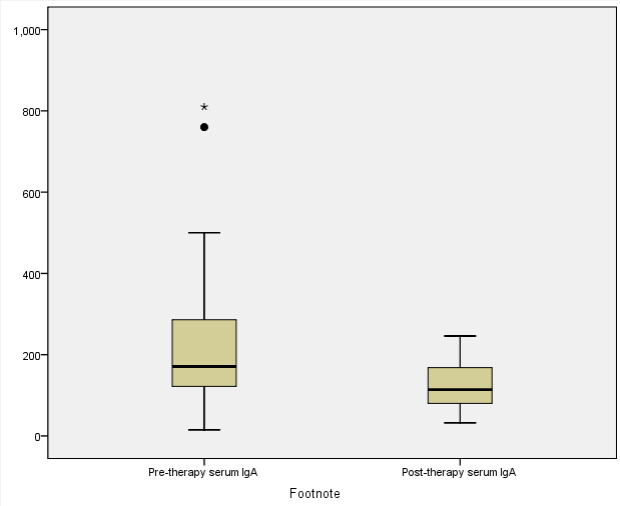

Figure 4 Changes in serum IgA levels pre- and post-therapy in CMI patients.

dL). The post-therapy mean serum IgA was significantly lower than the pretherapy value (t = 4.64, p < 0.000) [Figure 4]. Similar to what was found with serum IgG levels, 20% of our subjects had elevated serum IgA levels 6 months after treatment while 80% (40/50) of patients had reduced values.

The mean pre-therapy serum IgM levels in our subjects was 234.88 ± 115.28mg /dL with range of 428.00mg/dL (median = 220.00mg/dL); while the post-therapy mean value was 276.60 ± 148.62mg/dL with a range of 491.00mg/dL (median = 278.00mg/dL). No significant difference was observed. However, 32% (16/50) actually had reduced serum levels after 6 months of therapy. As found with IgG and IgA results, 68% (34/50) of them had higher serum IgM after 6 months of treatment.

Except for the serum IgG level, a comparison of the immunological and haematological parameters of patients in remission with those that were not in remission did not show any significant difference [Table 5].

DISCUSSION

The initial treatment with Hydroxyurea in the CML management as occurred in this study is not unusual [15], as it takes some time for newly diagnosed patients to be investigated and confirmed Philadelphia chromosome or BCR/ABL positive, a prerequisite for the use of Imatinib mesylate. Pending this confirmation, patients need some form of cytoreductive therapy to prevent complications such severe anaemia or hyperviscosity syndrome arising from uncontrolled abnormal white blood cells expansion.

The significant reduction in the absolute lymphocyte and CD4+ T lymphocytes counts post therapy recorded in the this study though in support of an earlier preliminary study carried out by these authors [7]. In view of the fact that other studies have shown significant cytoreductive effects of HU on absolute lymphocyte count, CD4+ T cells, and memory CD4+ and CD8+ T cells compared to those patients on placebo [16], it may, therefore, be a cumulative effects of both Hydroxyurea and Glivec that were responsible for the significant drop in ALC and CD4+ T lymphocytes counts observed in this study. Studies have shown that Imatinib mesylate can inhibit proliferation and function of lymphocytes [10,17,18]. However, despite the reduction the CD4+ lymphocytes and the ALC, and also a significant reduction absolute neutrophil count, infection was not recorded in our cohort during the period of follow-up; possibly because the values were still essentially above values that can predispose them to serious clinical infections. This finding suggests that infections are not a significant problem in patients treated with Glivec and tyrosine kinase inhibitors in general; and this is similar to the Italian experience of Breccia et al [19]. Another positive factor in this cohort of patients is that the majority have no risk factor for the development of infection.

In this study, prior to the commencement of Imatinib mesylate therapy, none of the patients had IgG hypogammaglobulinaemia, but 2 patients had reduced serum levels of IgA, while one had IgM hypogammaglobulinaemia. This is comparable to the findings of Steegmann et al [10] who did not also report IgG hypogammaglobulinaemia, but with only one patient with low IgA and 17 patients with low IgM. A comparison of the mean immunoglobulin values in chronic phase, accelerated phase and after six months of therapy showed that serum levels of IgA are normal in chronic phase, but are significantly reduced as a result of disease progression and with drug usage. The import of this is that patients may be prone to mucosal infections, particularly respiratory tract infection; suggesting that this should be looked out for while patient is on this drug. On the other hand, both IgG and IgM were relatively reduced in chronic phase but increased during disease progression and drug usage. Though IgG and IgM are known to be crucial in combating microbial infections, the mechanism by which they are preferentially stimulated and become more abundant as the disease progresses or as a result of drug therapy is not clear.

As documented by other workers, this study also showed certain percentage of patients with reduced immunoglobulins (IgG = 58%; IgA = 80%; and IgM = 32%) after therapy. The precise mechanism of this reduction associated with Imatinib mesylate usage in some patients, as also reported by other workers [9-11] has not been clearly unraveled. However, some workers have linked it to the inhibitory effects of Imatinib mesylate on B

Table 4: Comparison of immunological parameters of CML patients pre- and 6 months into Imatinib therapy.

Parameters value	Mean Pre-Therapy	Mean Post-Therapy	t	p
ToP (g/L)	75.52	72.40	1.79	0.080
Alb (g/L)	36.80	35.82	1.38	0.174
Glo (g/L)	38.68	36.78	1.10	0.277
IgA (mg/dL)	236.92	120.62	4.64	0.000
IgG (mg/dL)	1984.60	2067.72	-0.36	0.718
IgM (mg/dL)	234.88	276.66	-1.86	0.068

Reference values:
IgA: 40 – 230mg/dL; IgG: 688 – 1600mg/dL; IgM: 65 – 400mg/dL [1] Oyeyinka et al
Total protein: 58 – 60g/L; Albumin: 35 – 50g/L; Glo: 20 – 45g/L (OAUTHC, Ile-Ife Reference values)

Table 5: Comparison of haematological and immunological parameters of CML patients in remission and those not in remission.

Parameter t-value	In Remission p-value	Not In Remission	F-value
PCV (%) -0.46	35.74 ± 5.63 0.65	36.60 ± 7.11	0.90
WBC (/µL) -2.08	4,827.71±1716.97 0.56	14,120.27 ± 17263.67	42.91
PLT (/µL) -1.87	190,685.71±123966.00 0.08	382,033.33±387738.00	31.32
ESR (mm/hr) -1.003	26.77 ± 25.87 0.32	34.67 ± 25.64	0.001
CD4+ (/µL) -0.71	993.97 ± 464.53 0.48	1,094.00 ± 432.94	0.27
ToP (g/L) 1.28	73.37 ± 8.06 0.21	70.13 ± 8.47	0.001
Alb (g/L) 1.88	36.60 ± 3.73 0.67	34.00 ± 5.95	1.82
Glo (mg/dL) 0.39	37.06 ± 7.94 0.69	36.13 ± 6.67	0.35
IgA (mg/dL) -0.08	120.20 ± 57.44 0.94	121.60 ± 57.16	0.26
IgG (mg/dL) 2.01	2263.37 ± 1267.35 0.05	1611.20± 940.99	4.29
IgM (mg/dL) 0.07	275.69 ± 148 0.94	16278.93 ± 154.87	0.18

Reference values: IgA: 40 – 230mg/dL; IgG: 688 – 1600mg/dL; IgM: 65 – 400mg/dL [1] Oyeyinka et al. Total protein: 58 – 60g/L; Albumin: 35 – 50g/L; Globulin: 20 – 45g/L (OAUTHC, Ile-Ife Reference values)

lymphocytes [9] and T lymphocytes activation and proliferation [20]. T lymphocyte is particularly needed by the B lymphocytes for its maturation and immunoglobulin synthesis [21]. The BCR/ABL oncoprotein has also been found to inhibit the interaction between the stromal derived factor (SDF)-1 and its receptor, which lead to impaired B cell differentiation and maturation [17]; all these might lead to defective immunoglobulin production. Unlike the globulin fraction, serum albumin was found to be reduced pre-therapy. Since leukaemic cells can infiltrate the liver [21] which is the main site of albumin production, this could cause destruction of the hepatocytes and a reduced production capacity of albumin.

CONCLUSION

Not many research works has been done on the immunological effects of Imatinib mesylate in CML patients in Nigeria; as the drug is just been made available in the country about a decade ago through Glivec International Patient Assistance Programme (GIPAP). However, this work has found some of the effects of the drug recorded by other workers in the Caucasian studies, particularly its effects on serum immunoglobulins and CD4+ T lymphocytes and the possible predisposition to infection. It would have been more informative to determine the subset of CD4+ cells or other subsets of T lymphocytes affected by Glivec. A future study should determine if there are altered immune responses associated with Glivec therapy. This should be taken into consideration and adequate prophylaxis or treatment instituted when they arise.

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Conflict of Interest

Novatis donated the drug (Glivec; Imatinib mesylate) gratis to the patients through GIPAP (Glivec International Patients Assistant Programme).

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