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The use of Imatinib mesylate in Nigerians with chronic myeloid leukemia

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Summary

Objectives: To assess response and toxicity to Imatinib mesylate (Glivec) in Nigerian Patients with chronic myeloid leukemia.

Methods: From August 2003 to August 2007, 98 consecutive, consenting patients, 56 (57%) males and 42 (43%) females, median age 36 years (range, 11-65 years) diagnosed with CML, irrespective of disease phase received Imatinib at a dose of 300-600mg/day at the OAU Teaching Hospitals, Nigeria. Response to therapy was assessed by clinical, haematological and cytogenetic parameters. Blood counts were checked every two weeks in the first three months of therapy. Chromosome analysis was repeated sixth monthly. Overall survival (OS) and frequency of complete or major cytogenetic remission (CCR/MCR) were evaluated.

Results: Complete haematologic remission was achieved in 64% and 83% of patients at one and three months, respectively. With a median follow-up of 25 months, the rates of CCR and MCR were 59% and 35% respectively. At 12 months of follow-up, OS and progression- free survival (PFS) were 96% and 91%, respectively. Achievement of CR at six months was associated with significantly better survival ($p = 0.043$).

Conclusions: Compared to treatment outcome with conventional chemotherapy and alpha interferon, as previously used in Nigeria, the results obtained with this regimen has established Imatinib as the first-line treatment strategy in patients with CML, as it is in other populations, with minimal morbidity.

Keywords: imatinib mesylate, chronic myeloid leukemia, Nigeria, cytogenetic remission

Introduction

Chronic myeloid leukaemia (CML) has an annual worldwide incidence of 1/100,000, with a male: female ratio of 1.5:1. The incidence rises slowly with age to reach a median of about 60 years [1]. The median age of patients with CML in Nigeria and other African countries with a similar demographic pattern is 38 years [2,3]. Fleming and Menendez reported that more native African patients under age 40 years suffer from CML than any other group in the world; this differential age incidence pattern of CML is believed to be due to the age distribution of African populations rather than any inherent biological characteristic [4]. In the USA however, the incidence of CML in the age group under 70 years is higher among the African-Americans than among any other racial/ethnic groups [5]. It is probable that a combination of environment and as yet unknown biological factors may account for the differential age incidence pattern of CML between the Blacks and the other races in USA.

The advent of Imatinib, an orally available, small molecule signal transduction inhibitor (STI) that specifically targets protein tyrosine kinases (TKIs), in particular, the CML-related bcr-abl, has led to radical changes in the management of CML following the publication of several studies that confirmed superior clinical, haematologic and cytogenetic remissions when the drug was compared to IFN-α and ara-C in all phases of the disease [6-9]. Imatinib has become the first-line therapy for CML in the world, allogeneic stem cell transplantation now being reserved mainly for younger patients with poor-risk disease or for those who are resistant to Imatinib and/ or second generation TKIs [8,9]. With the availability of free Imatinib Mesylate in resource-poor countries (through donation from the Glivec international patient-assistance program [GIPAP]; www.maxaid.org), this drug has also become the first-line therapy for CML in Nigeria; a great relief for patients in resource-limited countries.

This report describes the results for patients with newly diagnosed CML in diverse phases of the disease that were treated with Imatinib.

Patients and Methods

Between August 2003 and August 2007, a total of 98 consenting adults and children, who had been diagnosed with CML, were commenced on Imatinib as part of the ongoing GIPAP treatment programme at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Nigeria. Eighty-four patients had been exposed to previous single-agent chemotherapy comprising: hydroxyurea (n = 79), busulphan (n = 5) and IFN-alfa (n = 5). Five patients had previously received concurrent multiple chemotherapeutic agents, including Cyclophosphamide, Oncovin, ara-C and prednisolone (COAP; n = 4) and Doxorubicin and ara-c (DA; n = 1). Participants were drawn from all parts of Nigeria. The diagnosis of CML was made according to the WHO standard clinical, haematologic and cytogenetic criteria [10], which has also been applied to the staging of the diseases in Imatinib era [11].

Chromosome analysis was done using cultured bone marrow aspirate samples; Philadelphia chromosome was estimated from at least 20 metaphases and the proportion of Ph+ cells was noted for each patient.

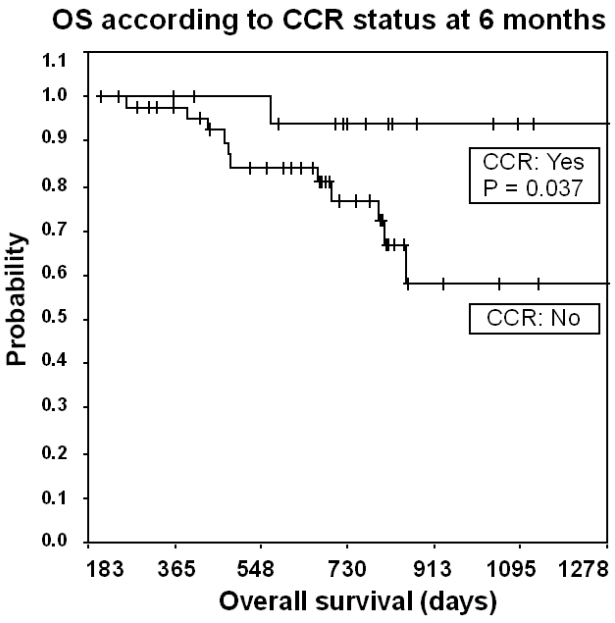
Patients in chronic phase received oral Imatinib: 400mg daily. Those in the accelerated or blastic phase received 600mg daily. Imatinib was continued for as long as there was evidence of continued benefit from therapy. Allopurinol (300 mg daily) was given until leucocyte count fell below 20 x 10^9/L. Patients with hyperleucocytosis (leucocyte count > 100 x 10^9/L), and on hydroxyurea, were continued on the latter for another 1-3 weeks, with monitoring of the full blood count before final withdrawal of the drug, when the white cell count fell to less than 100 x 10^9/L.

In individuals with severe Imatinib-induced myelosuppression, the drug was withheld until the neutrophils rose to 1.5 x 10^9/L and the platelets to at least 75 x 10^9/L. Patients with recurrent, therapy-induced myelosuppression had the Imatinib dose reduced to 300mg daily until blood counts normalised (minimum dose for therapeutic blood levels in adults). However, if the myelosuppression was related to blastic transformation, Imatinib was continued with appropriate supportive therapy being given.

Response to therapy was assessed by clinical, haematologic and cytogenetic parameters as recommended by the expert panel of the European LeukemiaNet [12]. Clinical examination and full blood count monitoring were performed every 1-2 weeks for the first three months, until the blood count became stable, or until remission was achieved. Thereafter, patients were monitored every three months. Serum chemistry and cytogenetic analyses were evaluated every six months.

Previously published definitions of CP, AP and BP were used [10,11]. Overall survival (OS) was the primary end-point and was defined as the interval between the date of commencement of Imatinib and the date of death or loss to follow-up. Secondary end-points were time to complete haematologic remission (CHR) and/or complete cytogenetic remission (CCR). CHR was defined as restoration of a normal blood count, with absence of blasts or promyelocytes, extramedullary deposits, or other signs of the disease. Cytogenetic response was checked every 6 months, by counting proportions of Ph+ cells from among not less than 20

Figure 1. Overall survival of patients according to attainment of complete cytogenetic remission (CCR) at 6 months



metaphases, whilst definitions of complete, major, minor and no cytogenetic response (CCR (0% Ph+), MCR (1-34% Ph+), mnCR (35-90 Ph+), and NCR (> 90% Ph+) and those for complete or major molecular response (CMR, MMR) were as previously described [12].

This study was conducted according to the declaration of Helsinki concerning patients' rights and confidentiality. Approval for the study was obtained from the OAUTHC ethical committee. All patients or their parents (in the case of minors) gave written informed consent.

The study is ongoing but for the purpose of this analysis, August 31st 2007 was taken as the cut-off, this being the date on which the first patient has been followed-up for 48 months. Analyses of OS and PFS were performed using the Kaplan-Meier method, by „intention-to-treat". Differences between subgroups of patients receiving Imatinib were analysed using the Log-rank test. SPSS for Windows 11 (SPSS Inc. 1981-2001, USA) and Microsoft Excel were used for all statistical calculations. The following pre-treatment variables were analysed for correlations with achievement of response, OS and PFS: age, gender, time of starting treatment and platelet count prior chemotherapy.

This study was based on 98 patients, their ages ranging from 11 to 65 years (median = 36). There were 56 males and 42 females. The median time from diagnosis to treatment was 14.3 weeks (range 0-239 weeks). Seventy-eight (80%) and 40 (41%) of 98 patients presented with splenomegaly and/ or hepatomegaly, with a median size of 12cm and 7cm below the costal margin, respectively; 85 (86.7%) patients were in CP and 13 (13.2%) in AP/BP (12 and 1 respectively, Table 1).

Table 1. Patients' characteristics at diagnosis

Variables	No.	Median	(Range)
Age, years: Patient	98	36	(11-65)
Gender: Male/Female (%)	56/42	(57/43)	
Splenomegaly (cm, BCM[1])	78	12	(2-34)
Days from diagnosis to start of Imatinib	98	100	(0-1673)
Percent peripheral blasts (%)	88	1	(0-34)
Platelet count (x 109/l)	87	248	(30-998)

[1] BCM = below the costal margin.

With a median follow-up of 25 months, 51 patients had repeat chromosome analysis at least 6 months into Glivec therapy; 30 (59%) and 18 (35%) achieved CCR and a MCR, respectively.

Also notable was the fact that on completion of one and three months of Imatinib therapy, 53/83 (64%) and 58/70 (83%) of patients respectively were in complete haematologic remission (CHR).

Kaplan-Meier analysis of the relevant pre- and post-recruitment variables shows that commencement of Imatinib within 60 days of diagnosis, and achievement of CHR within one month of commencing therapy were predictive for achieving a CCR ($p = 0.039$ and 0.019 respectively; Table 2).

Kaplan-Meier estimates for OS and PFS at one year were 96% and 91%, respectively. At 40 months, the OS and PFS had dropped to 68% and 61%, respectively. Eighty-seven of the 98 patients overall (88.8%) remain alive, and are tolerating the drug well.

Also, achievement of CHR within 3 months or CCR within 6 months of commencing therapy predicted for better OS and PFS (CHR: $p = 0.027$, 0.011 respectively; CCR: $p = 0.043$, 0.045 respectively; Table 2). A statistically insignificant trend ($p = 0.06$) was observed for better OS in patients who did not experience myelosuppression (requiring cessation of the drug for ≥ 2 weeks) during the first 6 months of treatment. Eleven of the 44 patients (25%) who were in MCR/mnCR at six months had improved to CCR at the last follow-up.

Discussion

With a median follow-up of 25 months, these results demonstrate a CCR rate of 59%, which is the same as that reported by Kantarjian et al in a previous study with 18 months' follow-up [13]. The latter group of patients had however previously received IFN-α, whereas most of the Nigerian patients had been treated with hydroxyurea as first-line therapy. Overall, 80% of newly diagnosed patients with CML in chronic phase would be expected to achieve CCR with Imatinib [14]. In this study, relatively shorter survival was to be expected, since 21 patients were not in chronic phase at the time of starting treatment, and responses are known to be less durable in AP and almost always transient in BP [8,15,16].

The median time from diagnosis to commencement of Imatinib was relatively long, at 14.3 weeks (range 0-239 weeks) and it is known that this can worsen the prognosis and reduce the probability of response. Nonetheless, the relatively high survival (96%, SE = 0.022) at one year is impressive for an African population of patients, although obviously, this value will fall with longer follow-up, with 68.3% at 40 months. The extended IRIS study has recently reported a 5-year overall survival estimate of 89% [17] and several studies have demonstrated significant survival differences based on the Sokal and/or Hasford risk groups at diagnosis [14,15,18-20]. However, these parameters could not be evaluated since initial data (at diagnosis) on the majority of our patients were unavailable.

The survival advantage observed for patients in whom CCR was achieved by six months is an important finding since it confirms the efficacy of Imatinib, an observation that has not been reported in native sub-Saharan Africans before. This pioneering work has shown that outcome of Imatinib therapy for Ph+ CML in native Nigerians is no different from reports in the Western populations.

We conclude that Imatinib in Nigerian patients with CML is very promising with the additional advantages of oral availability and tolerability, both of which make the drug highly acceptable.

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Table 2. Univariate analysis of patients characteristics, survival and cytogenetic remission

Variables*	p-Values					
Survival statistics	**OS**	**SE**	**PFS**	**SE**	**CCR**	**No. (%)**
At 1 year	**96%**	**0.022**	**91%**	**0.031**	**At 6 mo**	**20/63 (32)**
At 2 years	80.9%	*0.051*	70.7%	0.059	**At LFU**	**30/51 (59)**
At 40 months	68.3%	*0.073*	60.7%	0.069		
Parameters at recruitment	**No.**	**OS**	**No.**	**PFS**	**No.**	**CCR**
Gender: male / female	56/42	ns	53/41	ns	28/23	0.066
Age (years)						
≤ 30 / > 30	31/67	ns	29/65	ns	13/38	ns
≤ 38 / > 38	57/41	ns	54/40	ns	30/21	ns
Days from diagnosis to start of Imatinib						
> 60 / ≤ 60	64/34	ns	62/32	ns	31/20	**0.039**
> 150 / ≤ 150	41/57	ns	41/53	ns	20/31	**0.012**
Platelet count (x 109/l)						
≤ 250 / > 250	46/41	ns	45/40	ns	28/18	ns
≤ 400 / > 400	65/22	ns	63/22	ns	37/9	ns
Parameters post-recruitment	**No.**	**OS**	**No.**	**PFS**	**No.**	**CCR**
Haematologic status						
CHR at 1 month: Yes / No	53/30	ns	51/29	ns	33/15	**0.019**
CHR at 3 months: Yes / No	58/12	**0.027**	56/11	**0.011**	35/3	ns
MS >2 wks in the first 6 months: No/Yes	64/21	0.070	61/21	ns	39/11	ns
Cytogenetic status						
CCR at 6 mo: Yes / No	19/44	**0.043**	19/43	**0.045**	NA	NA
		No.	**(%)**		**No.**	**CCR**
CCR / MCR / mnCR at LFU		**30/18/3**	**(59/35/6)**		NA	NA
CCR / MCR / mnCR at 6 months		**19/37/7**	**(30/59/11)**		NA	NA

p-Values in bold type are significant, those in regular type are close to significance.
*The variables with the better outcomes are written first.
Abbreviations: OS, overall survival; PFS, progression-free survival; SE, standard error; BCM, below the costal margin; LFU, last follow-up; ns, not significant; NA, not applicable; CHR, complete haematologic remission; CCR: complete cytogenetic remission; MCR: major cytogenetic remission; mCR: minor cytogenetic remission.

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Применение Иматиниба мезилата (Гливека) у нигерийцев с хроническим миелолейкозом

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Резюме

Цель работы: Оценить клинический ответ и токсичность иматиниба мезилата (Гливека) у нигерийских больных хроническим миелолейкозом (ХМЛ).
Методы и клинический материал: С августа 2003 г. по август 2007 г. под наблюдением находились 98 больных с диагнозом ХМЛ (средний возраст 36 лет – от 11 до 65 лет), позитивных по Ph/bcr-abl, давших согласие на терапию, в том числе 56 мужчин и 42 женщины. Независимо от фазы заболевания, лечение Иматинибом проводилось в дозах 300-600 мг в день в госпитале OAU (Нигерия). Ответ на лечение оценивался по клиническим, гематологическим, цитогенетическим и/или молекулярным параметрам. Число клеток в крови проверяли каждые 2 недели в течение первых трех месяцев терапии. Кариотипирование повторяли каждые 6 месяцев. Регистрировали общую выживаемость и частоту полной гематологической ремиссии (ПГР) или большой цитогенетической ремиссии (БЦР, 1-34% Ph+ клеток).
Результаты: После 1 и 3 месяцев лечения полная гематологическая ремиссия была достигнута, соответственно, у 64% и 83% больных. При среднем сроке наблюдения 25 месяцев, частота ПГР и БЦР составляла 59% и 35%, соответственно. Спленомегалия и/или гепатомегалия менее 7 см от края ребер были прогностическими признаками в отношении ПГР (соответственно, p = 0.0006 и 0.034). После 12 месяцев наблюдения, общая выживаемость и выживаемость без прогрессии (ВБП) составляла, соответственно, 96% и 91%. Число бластных форм на периферии ниже 5% на момент диагноза и достижение ПГР через 6 мес. были ассоциированы со значительно лучшим выживанием (уровни p были, соответственно, 0.037 and 0.043).
Выводы: В сравнении с обычной химиотерапией и применением альфа-интерферона, как было ранее показано в Нигерии, иматиниб может индуцировать раннюю цитогенетическую ремиссию у Ph/bcr-abl- позитивных больных ХМЛ, при минимальных (побочных) заболеваниях.

Ключевые слова: иматиниб мезилат, хронический миелолейкоз, цитогенетическая ремиссия