EFFECT OF COVID-19 PANDEMIC ON ACCESS TO TYROSINE KINASE INHIBITORS IN NIGERIA

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ABSTRACT

Background:
Accessing Tyrosine Kinase Inhibitors (TKIs) during COVID-19 pandemic-related lockdown threatened the abysmally low adherence to therapy in Nigeria. An alternative means of getting medications to the beneficiaries by courier was assessed.

Aims and Objectives:
To assess clinic attendance of patients on TKIs during COVID-19 pandemic lockdown in relation to pre-COVID era; the measures taken to ensure safe delivery of TKIs to the door-step of patients on these medications nationwide; and the outcome.

Materials and Methods:
Clinic attendance of all active patients with chronic myeloid leukaemia (CML), gastrointestinal stromal tumours (GIST), or chronic eosinophilic leukaemia (CEL) on TKIs was assessed from January to September 2020. In collaboration with the Pharmacy Department, a reliable courier service was engaged to deliver TKIs to the door step of patients with informed consent during the lockdown period. Account of drugs posted and the latest full blood count results of patients were obtained and documented appropriately.

Results:
A total of 862 out of 935 registered patients, accessed TKIs during the period of evaluation between March and September 2020; 569 (66%) used courier service, while 220 (25.5%) attended outpatient clinics and 73 (8.5%) were lost to follow up. The majority of the courier users, 219 (38.5%) were from South West (SW), while the least, 30 (5.3%) were from North East (NE). Clinic attendance for April (21) and May (43) during the lockdown was low compared to the average monthly attendance before lockdown (January to March; 174). There was a significant difference in the use of courier service ($\chi^2 = 34.815$; $p = 0.001$) and clinic attendance ($\chi^2 = 27.000$; $p = 0.001$) when compared with the number of patients registered per region.

Conclusion:
The lockdown period impacted very negatively on clinic attendance and the engagement of a courier service facilitated home delivery of TKIs at the peak of COVID-19 pandemic in Nigeria. This method may be further explored to improve adherence to therapy going forward.

Keywords: COVID-19, tyrosine kinase inhibitors (TKIs), Nigeria.

INTRODUCTION

The cytoreductive busulphan and hydroxycarbamide were the main therapeutic agents for the incurable Ph/BCR-ABL1+ chronic myeloid leukaemia prior to the introduction of allogeneic stem cell transplantation and interferon alfa in the 1980s and 1990s (CML).[1-5] Patients on cytoreductive chemotherapy achieved partial cytogenetic remission without cure, with an overall survival of 3-6 years for patients presenting in chronic phase compared to a few months in those presenting in the more advanced accelerated phase or terminal blastic phase.[1,2,3] Allogeneic transplantation is potentially curable, but limited to the availability of compatible donors and the development of life-threatening graft versus host disease (GVHD).[4]

Alfa interferon has been associated with cytogenetic remission and generally prolonged survival, adherence is poor because of its intolerable adverse effects and parenteral administration.[5,6]

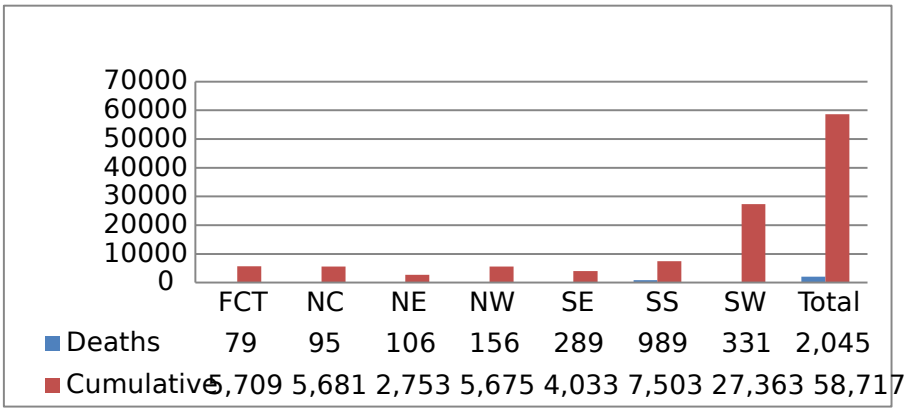
The approval of imatinib mesylate by the US Food and Drug Administration in 2001 changed the natural history of CML positively to become a chronic disease with encouraging survival for all phases of the disease.[7-9] The median survival of patients in chronic phase on imatinib or any of the second generation TKIs (dasatinib, nilotinib, bosulif) is now estimated at 25–30 years compared to only 3-6 years of the pre-imatinib era.[3,4,10] Tyrosine kinase inhibitors have now replaced allogeneic stem cell transplantation as frontline therapy for chronic myeloid leukaemia and they have also been approved for other haematologic cancers and solid tumours, such as, Philadelphia-positive acute lymphoblastic leukaemia (ALL), chronic eosinophilic leukaemia (CEL) and gastrointestinal stromal tumours (GIST).[11]

Despite this innovative treatment, most individuals suffering from CML in Nigeria had no access to any TKIs until the Max Foundation (now Mass Solution) set up Novartis Pharmaceuticals-supported Glivec International Patient Assistance Program (GIPAP). This programme that started in Nigeria in 2003 provides patients in low-and middle-income countries (LMICs) free access to imatinib for life.[8] Since inception, the programme has provided imatinib mesylate and other second generation TKIs to more than 1500 and 50 patients respectively from across the Nigeria.

Over the years, it has been observed that patients on TKIs must ensure over 95% adherence to achieve optimal remission, the key to successful treatment outcome.[12] Unfortunately, adherence to imatinib among patients in Nigeria is abysmally low at 47%.[13] The major militating factors are poverty, general ignorance, high cost of transportation to the only treatment centre in the country, Ile-Ife, Osun State, SW Nigeria and forgetfulness.[14] Good family support has, however, been reported to be central to promoting adherence to therapy among Nigerian patients.[13]

The dreaded novel coronavirus 2019 (COVID-19) was first reported in December 2019 from Wuhan, China by the Chinese Center for Disease Control and Prevention (CDC) as a highly contagious **"**pneumonia of unknown aetiology".[15] The virus was also named as *severe acute respiratory syndrome* coronavirus-2 (*SARS-CoV2*) because of its similarity to the coronaviruses responsible for the SARS-CoV epidemics of 2002/2003 in China and Canada, and the Middle East respiratory syndrome coronavirus (MERS-CoV) of 2012 in Saudi Arabia.16-18 COVID-19 is a natural zoonotic envelope RNA-Coronavirus, with bats as primary host; 66% of the original 41 victims of Wuhan COVID 19 epidemic had history of exposure to Hunan seafood wholesale market, raising the possibility of animal to human transmission.[15-18]

The World Health Organisation (WHO) declared COVID-19 a pandemic on the 11th of March 2020, following an exponential rise in human to human transmission to 118,000 individuals across 114 countries, with 4,291 mortality, within 3 months of the outbreak.[19] Globally, as at 30th September 2020, there were



(*Computed from Week 40 Report on covid19.ncdc.gov.ng*)

Figure 1. COVID-19 Confirmed and Mortality Nationwide Cases in Nigeria across the Geopolitical Zones (Feb-Sept, 2020)

33,502,430 cases with 1,004,421 deaths (3.0% case fatality rate) and a total recovery of 32, 498,009. (covid19.ncdc.gov.ng). The first case in Nigeria was confirmed in a 44-year-old Italian visitor on 27th February 2020. The virus spread throughout the country and soon became a community acquired infection with total confirmed cases of 58,848, mortality of 1,112 and a case fatality rate of 1.9% by 30th September 2020.[20] More males (64%) were infected than females (36%) with the prevalence being more in the 31-40 years age bracket (*covid19.ncdc.gov.ng*). Figure 1 shows the national distribution of COVID-19 infection with Lagos, SW Nigeria, constituting the epicenter. The total period of lockdown was between 30 March 2020 and 27 July 2020. Local flights and the Kaduna-Abuja rail line were restored on the 26th of July.

COVID-19 infection may be considered generally, a mild disease with a low case fatality rate of 2-5% as compared to 10% and 34% associated with the SARS-CoV and MERS-CoV, respectively.[19] Although the 2-5% case fatality rate indicates that over 95% of persons infected with the virus would recover fully. However, the loss of a single person to a preventable disease is not acceptable.

COVID-19 pandemic has impacted very negatively on global health, in particularly the management of patients living with chronic non-communicable diseases (NCDs) like HIV/AIDS, tuberculosis, hepatitis, diabetes, hypertensive heart disease, chronic pulmonary diseases, psychiatric disorders and malignancies.[21] The immunosuppression associated with the stress of the pandemic has been reported to have a negative effect on the healing process of chronic disorders and recovery.[21] Even, healthcare providers, were not spared, they were getting infected every day and are dying of the disease, especially in the setting of insufficient provision of personnel protective equipment (PPE). The lockdown imposed on account of the pandemic also significantly impacted the global economy negatively, thus affecting all social strata.

The health sector was obviously not left out since patients were unable to access their medications because of the unexpected COVID-19 related restriction of movement that starting on 30th March 2020 in Nigeria. Both interstate and intrastate forms of transportation were affected, even, air flights were not available for the very few patients that could afford to travel by air. This, therefore, became another limiting factor to the adherence patients to therapy. The aim of this study was to assess the effectiveness of the use of an alternative means of getting TKIs to the hands of beneficiaries.

MATERIALS AND METHODS

This is a retrospective and prospective study of the active patients on TKIs attending the Haematology Clinic, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Osun State, Nigeria, between January and 29 March 2020 (retrospective) and 30 March and 30 September 2020 (prospective). With the approval of the Director of Pharmacy and the Programme Pharmacist, a reliable courier service was identified and the beneficiaries were notified through their treatment group, *the MaxCare Support Group*. Informed consent was obtained to share contact details of patients with the courier service. The charges were negotiated between the courier service agent and individual beneficiaries. Courier charges ranged from ₦2500 ($6.5) for the SW States to ₦ 8,500.00 ($21.8) for the far North. Data obtained included the number of active patients with CML, GIST, or CEL on TKIs, their state of origin; number of clinic attendance between January 2020 and September 2020, number lost to follow-up and whether or not a courier service was utilized. The full blood counts (FBC) of patients were obtained online or through the courier service and results and prescriptions were recorded appropriately.

RESULTS

Figure 2 summarises the clinic attendance for the period January to September 2020 including the lockdown period from 30th March through to 27 July 2020. The clinic attendance in April (21) and May (43) were very low compared to the average monthly attendance of 174 to access TKIs between January to March 2020 (162-188) before the lockdown. Clinic attendance has continued to increase gradually since the lifting of the lockdown.

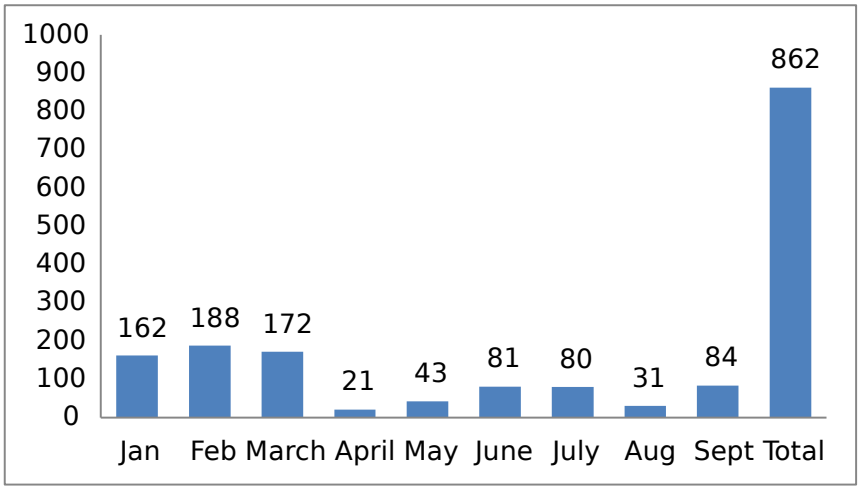


Figure 2. Haematology Clinic attendance before and after COVID-19 lockdown (Jan-Sept, 2020)

The numbers of active patients on TKIs in the centre were 935 as at January 2020. The majority were from the SW with 379 (40.5%), out of whom a total of 355 (93.7%) were either seen in person at the clinic (38.3 %) or received their drugs by courier (61.7%). The NE had the least number of registered patients with 55 (5.9%) out of whom 50 (90.9%) were seen in person (40.0%) or received their drugs by courier (60.0%). The SS, NC, FCT, SE and NW had 122 (13.0%), 111 (11.9%), 94(10.0%), 96 (10.3%) and 78 (8.3%) registered patients, out of whom 46 (46.0%), 31 (30.1%), 21 (23.9%), 28 (30.1%) and 11 (15.1%) were seen in person and 54 (54.0%), 72 (69.9%), 67 (76.1%), 65 (69.9%) and 62 (84.9%) were seen by courier respectively (Figure 3).

A total of 862 of the active 935 patients, accessed TKIs during the period of restriction and up until 30th September; 569 (66%) used the courier service and 293 attended outpatient clinics (routine clinical services were available during the lockdown). Three (3.2%) of 95 patients from the South East region and two (0.9%) of 219 courier users from the South West were unable to pay for the service and subsequently remained without medications until it was sent via another patient who was seen in the outpatient clinic from their place of domicile.

Fifteen patients (12 with CML, 2 with GIST and 1 with CEL) on second line TKIs (Dasatinib, Bosutinib or Sunitinib) accessed TKIs during the period of this evaluation. The majority of the courier users, 219 (38.5%) were from SW and 30 (5.3%) from NE zone; the others were from FCT 67(11.8%), NC 72 (12.7%), SE 65 (11.4%), NW 62(10.9%) and SS 54 (9.5%) (Figure 3). The use of the courier service increased from 411(44.0%) at the end of July to 569 (60.9%) by the end of September 2020 after counselling.

Amongst 293 (33.9%) who attended the outpatient clinics, 136 (46.4%) were from the SW and the least were 11 (3.8%) and 20 (6.8%) from the NW and NE respectively. Others were from FCT 21 (7.2%), NC 31 (10.6%), SE 28 (9.6%), and SS 46 (15.7%; Figure 3)

A total of 73 (7.8%) patients of the 935 active patients were lost to follow up. Twenty four (32.9%) were from the SW and 3 (4.1%) were from SE others were from SS 22 (30.1%), NC 8 (11.0%), FCT 6 (8.2%), NE and NW had 5 (6.8%) each (Figure 3).

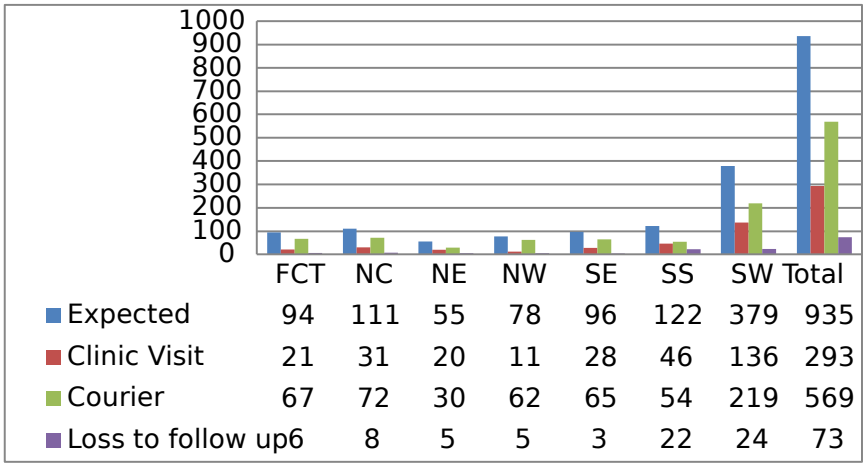


Figure 3. Nationwide distribution and mode of accessing TKIs during and after COVID-19 lockdown (χ^2 = 49.225; p = 0.001).

There were statistically significance relationships between the number of registered patients nationwide (expected) when compared to those who accessed TKIs by attending the clinic (χ^2 = 27.000; p = 0.001) or by using the courier service (χ^2 = 34.815; p = 0.001).

DISCUSSION

The COVID-19 associated inter- and intracity lockdown threatened the abysmally low adherence to TKIs in Nigeria, which was confirmed by Origbo *et al* to be 47%.[13] An attempt at tackling this brought about the initiative of using a courier service to send the medications to the door steps of patients. More than 80% of the expected patients were seen either in person or via the courier across the geopolitical zones. This is achieved due to counseling and re-counseling of the patients at every encounter in the clinic, via the support group platform, the *MaxCare,* Nigeria, on the need to adhere to medication for optimal molecular response.

The lost to follow up of 73 (7.8%) patients was most likely due to travel restrictions during this period, lack of access to information on the support group platform and probably financial challenges.

Soon after the initiative started, it was observed that poverty among some Nigerian patients accessing the drugs from the SE (3.2%) and SW (0.9%) could lead to the development of resistance, if there was no access to medications. Bolarinwa *et al* had earlier highlighted that poverty as one of the leading causes of poor adherence to the use of TKIs in Nigeria patients.[14] Counseling increased the awareness the patients such that the use of the courier service increased from 44.0% to 60.9% in the following three months.
More beneficiaries of the courier service were from the SW ($\chi^2 = 34.815$; $p = 0.001$) probably because the cost of the service was low, they were at close proximity to the only treatment centre in the country (OAUTHC, Ile-Ife) and they constituted the highest percentage of registered patients. The contrary could be said about the NE region, which is furthest away from the Ile-Ife, Nigeria, and from where fewer patients were registered and utilized the courier service. With the success of this innovation, we plan to maintain the service such that patients would only need to be physically present for clinical evaluation, karyotyping and molecular monitoring twice a year, instead of three or four times. Patients would also have the opportunity to attend the Haematology Clinic in their local hospitals from where they were referred in the first instance. The physical presence of patients at clinics, however, will also serve to confirm that they are alive and the drugs are not collected by ghosts.

The lockdown experience has shown that the request for decentralization of treatment centres for the benefit of patients domicile outside the SW Nigeria is possible through the courier service that has facilitated easy access to medication and thus promoting adherence.

The lockdown has adversely affected the followed up of patients for karyotyping and BCR-ABL1 monitoring of CML response to TKI therapy. This might lead to the delay in detecting the development of sub-optimal response or resistance to these drugs. The hospital has also lost some revenue in terms of consultation fees that should be paid by patients who attend the clinics; this is an inevitable SARS-CoV-2 pandemic-related economic loss to the hospital.

The COVID-19 pandemic movement restriction has impacted negatively on medical practice generally. The care of patients was adversely affected due to cancellation/postponement of scheduled surgery, because of lack of blood transfusion support due to non-availability of donors. Routine services and care were disrupted in many instances because some health care providers were infected with the virus and had to be in self-isolation. Akanmu and his group (2020) at the Lagos University Teaching Hospital (LUTH) reported that similar devastating effects on patients care resulted from COVID-19 pandemic-related disruptions of hospital services.[22] In the USA, decreases in emergency department visits were documented in five health care systems in Colorado, Connecticut, Massachusetts, New York, and North Carolina that ranged from 41.5% in Colorado to 63.5% in New York, with the most rapid rates of decrease in visits occurring in early March 2020, as the increase in the US case count for COVID-19 accelerated.[23] Similarly, UK workers had shown that the weekly data until April 2020 demonstrated significant falls in admissions for chemotherapy (45-66% reduction) and urgent referrals for early cancer diagnosis (70-89% reduction), when compared to pre-emergency COVID-19 levels in eight hospitals across the UK.[24] Management of patients with chronic diseases including cancer, diabetes, hypertension and sickle cell disease has also been adversely affected, because patients could not satisfactorily access therapy [21,22]; unfortunately, courier services could not be used to solve such problems.

Further negotiations with the courier service agent may be necessary, should there be a need for further use of this service, being the safest, quickest,

cheapest and most reliable means of getting the drugs to the patients under the prevailing circumstances and going forward.

CONCLUSION

The effect of intra- and interstate lockdown due to COVID-19 pandemic has created challenges in managing acute and chronic illnesses worldwide. Adopting home delivery of TKIs via a courier service was one option of mitigating some of the challenges. Poverty, however, contributed to the inability of some patients to use the courier effectively. This innovation could be extended to specialised drugs for patients living with some other chronic disorders.

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Conflict of interest:
The authors have no conflict of interest to declared.

Authors' Contributions:
The concept for the study was developed by MAD and OJO. MAD, OJO, NOA, RAAB, TOO, LS and OAO contributed to the design of the manuscript. MAD, OJO and NOA contributed to the writing of the manuscript. MAD, OJO, SOK, OTB, OAO retrieved the data. Data was analysed by MAD, OJO and NOA. All authors contributed to the management of the patients and review of this manuscript.

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