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Protocol

Improving treatment outcomes in chronic myeloid leukaemia patients using imatinib and artesunate combination therapy: a randomized controlled clinical trial protocol (IMART-trial)

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ABSTRACT

Background: Chronic myeloid leukaemia (CML) is a haematological cancer accounting for 15% of newly diagnosed cancers in adults. Imatinib, a tyrosine kinase inhibitor (TKI), has transformed a once-fatal disease into a manageable condition. However, about one-third of patients develop resistance to the drug, increasing the disease burden and risk of progression, especially in low-and middle-income countries where newer TKIs are expensive and limited. Artesunate, an antimalarial drug, has been reported to exhibit anti-neoplastic effects alone or in synergy with other anti-neoplastic agents.
Methods: This randomised controlled trial will evaluate the clinical efficacy of the combination therapy of imatinib and artesunate in imatinib-naive patients and sub-optimal responder patients as defined by the European LeukemiaNet. Patients will be given imatinib at 400 mg daily, while the test groups will also receive artesunate (200 mg daily for 14 days monthly). Serial clinical assessments, laboratory investigations and pharmacokinetic analyses will be conducted at 1, 3, 6, 9, and 12 months into therapy. The treatment outcomes for each patient will be determined using the complete blood count and BCR::ABL1 quantification.
Conclusions: An imatinib-artesunate combination therapy could be a cost-effective solution to the development of imatinib resistance in newly diagnosed CML patients and possible alternative option in the management of sub-optimal response to imatinib.
Trial registration: Trial registration number is NCT07022743.

Keywords: Imatinib-artesunate, Combination therapy, Chronic myeloid leukaemia, Suboptimal response, Drug repurposing

INTRODUCTION

Chronic myeloid leukaemia (CML) is a clonal disease of the pluripotential haemopoietic stem cells, caused by a reciprocal translocation between chromosomes 9 and 22 with resultant formation of *BCR::ABL1* chimeric gene and oncoprotein with constitutive tyrosine kinase activity.[1] Through constitutive stimulation of multiple signal transduction pathways, this tyrosine kinase leads to neoplastic myeloid lineage expansion, primarily the granulocytic series but also megakaryocytic and only rarely, erythroid cells. Tyrosine kinase inhibitors (TKIs)

is a game-changer in the management of CML, and patients now have a life-expectancy close to their age-matched controls.[2] Imatinib is the first-line therapy (TKI) for the management of Nigerian CML patients, which is consistent with recent guidelines on the management of CML.[3] Since 1998, when imatinib mesylate was first introduced, the treatment of CML has gained radical improvement with better outcomes.[4] Imatinib is available freely to patients in resource-limited countries such as Nigeria under the Glivec International Patient Assistance Program (GIPAP). A major limiting factor with this drug, however, is the development of resistance which makes long-term disease-free remission difficult in some patients. The proportion of patients who achieved clinical cum molecular response after one year and 5 years of standard dose imatinib daily ranged from 20% to 59% and 60% to 80% globally.[5] In Nigeria, only 39.4% of CML patients on imatinib achieved major molecular response at ≥18 months of therapy while 25% of patients had imatinib-resistance from BCR::ABL1 kinase domain mutations which explained the cause of unsatisfactory response in this category of patients.[6] Lewandowski and colleagues found twelve BCR::ABL1 mutations in 11 of 92 CML patients causing resistance to imatinib of which 40% were primary mutations while the rest 10.3% were secondary ones.[7]

Several approaches aimed at overcoming imatinib resistance in CML patients have been explored. These include dose escalation of the drug or switching the patient to a second or third-line TKI. The use of combinations of TKIs and interferon or pegylated interferon, omacetaxine mepesuccinate have been explored, while allogeneic stem cell transplantation following failure of TKIs has also been suggested to overcome the resistance.[6] However, in a resource-limited setting, these options are not easily obtainable due to cost and other limitations. Therefore, there is a need to continuously search for an affordable alternative, which artesunate potentially presents.

Treatment milestones in chronic myeloid leukaemia

Mutations in the kinase domain of BCR::ABL1 are often responsible for resistance to imatinib. However, it is not necessary to request mutation screening on a routine basis unless there is an indication for a loss of response.[8] The first therapeutic milestone is based on evaluation of the patient after 3 months of therapy. It is expected that a complete haematologic response (CHR) is achieved at this time for an optimal response.[9] A partial haematological response (PHR) after 3 months of standard dose of imatinib is considered a sub-optimal response according to the European Leukaemia Net (ELN) recommendations. [10]

At 6 months, a major cytogenetic response (MCyR) is expected for an optimal response, which is defined as fewer than 36% Ph-positive metaphases. A suboptimal response is defined as a minor or minimal cytogenetic response (36% to 95% Ph-positive metaphases), while no cytogenetic response implies treatment failure.[9] At 12 months, an optimal response is a complete cytogenetic response (CCyR), while a partial cytogenetic response (PCyR) means a suboptimal response.[9] At 18 months, optimal response is defined as a major molecular response (MMR), while complete cytogenetic response is equal to a suboptimal response.[11]

Complete cytogenetic remission (CCyR) is equivalent to BCR::ABL1 ≤1%, major molecular response (MMR) or MR^3 is defined as BCR::ABL1 transcript level ≤0.1% and MR^4 is defined as a BCR::ABL1 transcript level ≤0.01% or undetectable disease in cDNA with >10,000 ABL1 transcripts.[5] Treatment milestones and the definition of suboptimal response according to the European Leukaemia Net are summarized in Table 1.[10]

Table 1: Definition of suboptimal response and treatment milestones.

Timeline	Optimal response	Sub-optimal response	Treatment failure
3 months	CHR or Ph+≤35%, and/or *BCR::ABL1* ≤10%	3 months: Less than CHR or *BCR::ABL1* >10% and/or Ph+ 36-95%	3 months: Non-CHR and/or Ph+> 95%
6 months	6 months: PH+ 0%, and/or *BCR::ABL1* < 1%	*BCR::ABL1* 1-10% and/or Ph+ 1-35% (PCyR)	6 months: *BCR::ABL1* >10% and/or Ph+ >35% (<PCyR)
12 months	12 months: *BCR::ABL1*≤0.1%	12 months: *BCR::ABL1* 0.1-1%	12 months: *BCR::ABL1* >1% and/or Ph+ ≥ 1%
Any time	Any time: BCR::ABL1 ≤ 0.1%		Any time: Loss of CHR, Loss of CCyR Confirmed loss of MMR Mutations, CCA/Ph+

Drug repurposing: artesunate use in chronic myeloid leukaemia treatment

Drug repurposing is a strategy for identifying new uses for approved medications outside of the scope of their original indication for use.[12] Artesunate is a semi-synthetic artemisinin derivative and has been established as the first-line treatment for malaria.[13] However, it has been reported to possess anti-neoplastic effects either singly or in synergy with established anti-neoplastic drugs.[13] The potential use of artesunate in cancer has been explored and established by several studies.[14,15]

Artesunate has demonstrated evidence of anticancer activity by inducing apoptosis, differentiation and autophagy in colorectal cancer cells by preventing cancer cells from forming new blood vessels, inhibition of cell invasion and migration, inducing cell cycle arrest in sunitinib-resistant renal cell carcinoma, increasing reactive oxygen species (ROS) levels, regulating signal transduction pathway in human bladder cells and evidence of antitumor growth against urinary bladder and colorectal cancers have been established.[15,16] Also, artesunate has been shown to increase liver cancer cell sensitivity to sorafenib in advanced hepatocellular carcinoma through suppression of the MEK/ERK pathway.[14]

Artesunate also has immunomodulatory activity where immune cells are converted to an antitumor phenotype that can revert tumour-induced desensitization of immune surveillance, which helps with tumour regression.[17] In chronic myeloid leukaemia, *Artemisia vulgaris* methanol extract has been established to inhibit the activity of BCR/ABL, which is activated in over 90% of CML cases; thus, inhibiting molecular signalling such as AKT and MAPK leading to cytotoxicity through apoptosis.[18]

Von Hagens in a dose finding clinical trial defined a well-tolerated dose of oral artesunate as add-on therapy in patients with metastatic breast cancer to be up to 200mg/day (2.2-3.9mg/kg/day) oral artesunate and recommended this in phase II/III trials.[19] Oral artesunate at a dose of up to 200mg/day (2.2 - 3.9 mg/kg/day) was established to be safe and well tolerated over four weeks in colorectal and breast cancer patients without any significant toxicity.[20] In-vitro studies have shown tumour suppressive effect and induction of apoptosis in CML mouse models[21;] therefore, artesunate anti-cancer drug potentiation singly or in combination with other anti-cancer agents to give improved treatment is not in doubt. The mechanism of action of this artemisinin derivative is believed to be mainly due to endoperoxide-induced cytotoxicity via generation of reactive oxygen species when haemoglobin or ferrous iron activates the endoperoxide moiety of the drug.[21]

The selective toxicity of artesunate to tumour cells is partly explained by reduced levels of antioxidant enzymes (e.g., catalase, glutathione peroxidase, superoxide dismutase) in these tumour cells.[22] Artesunate may also express toxicity towards some specific tumour proteins or biomarkers. Eling and co-researchers demonstrated this when they showed that artesunate selectively had high toxicity towards pancreatic ductal adenocarcinoma cells expressing KRas oncogene but did not affect non-neoplastic human pancreatic ductal epithelial cells.[23]

Chen et al demonstrated that artesunate enhances cancer cell death by inhibiting glycolysis in adriamycin-resistant chronic myeloid leukaemia cells in vitro, thus confirming the molecular basis of artesunate in regulating glycolysis-related enzymes (MDR1 and ABCG2) in leukaemia cells.[24] However, it is presently unknown whether artesunate can augment imatinib activity in the treatment of CML. The affordability and good clinical tolerability of artesunate combined with its anti-neoplastic properties make it a suitable and worthwhile option for this clinical trial.

Research hypothesis

We hypothesize that the combination therapy of imatinib and artesunate will demonstrate superior efficacy than imatinib alone in newly diagnosed CML patients, i.e., earlier achievement of haematological and molecular remissions and lower incidence of resistance or treatment failure, and that the combination therapy will improve treatment outcome and halt disease progression in patients with suboptimal response to imatinib

Aim

Aim of the study is to evaluate the clinical effectiveness of an imatinib-artesunate combination therapy as compared with imatinib alone in newly diagnosed CML patients and its possibility as an alternative option in the management of sub-optimal response to imatinib in CML patients.

Objectives

The objectives of the study are to assess the safety of artesunate use beyond its traditional antimalarial dosing period in CML patients; compare treatment outcomes between patients on imatinib alone and patients on imatinib plus artesunate at 3, 6, 9, and 12 months of follow-up; determine the effect of imatinib and artesunate combination on the achievement of major molecular remission [MMR] in CML patients with sub-optimal response to imatinib; determine the effect of artesunate on imatinib pharmacokinetics following co-administration of the two drugs.

METHODS

The study shall be carried out at the Departments of Haematology and Blood Transfusion, Obafemi Awolowo University Teaching Hospitals Complex, and the

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines was used in the protocol development and reporting.[25]

Study design

The study is a prospective, open label, randomized phase 2 clinical trial of *Im*atinib and *Art*esunate combination therapy in chronic phase CML patients (IMART-Trial). Patients will be recruited and followed up for at least 12 months of imatinib/artesunate therapy. The study is a three-arm (groups) study; the first group (Group A) will include 25 newly diagnosed, imatinib-naive, chronic phase CML (CP-CML) patients who shall be placed on a standard dose of imatinib (400mg daily) alone. The second group (Group B) shall be 25 newly diagnosed, imatinib-naive, CP-CML patients who shall be placed on standard-dose imatinib (400mg daily) plus artesunate (200mg daily for 14 days every month). Patients will be assigned to either group A or group B by randomization generated by the clinical trial randomisation tool website. The third group shall be 25 imatinib-exposed CML patients who have shown evidence of sub-optimal response to imatinib therapy according to the ELN guideline.[5] This group shall have standard-dose imatinib (400mg daily) plus artesunate (200mg daily for 14 days every month). Suboptimal response as defined by inability to achieve complete haematologic response (CHR) at 3 months, major cytogenetic response (MCyR) at 6 months, complete cytogenetic response (CCyR) at 12 months or major molecular response (MMR) at 18 months of standard dose of imatinib therapy or patients whose CML is progressing and laboratory results indicates reversal of previously crossed milestones.[9]

Sample size determination

The sample size was determined by the formula for sample size calculation for comparison between two or more groups when the outcome variable of interest is qualitative using two-tailed statistical analysis.[26] This was based on a confidence interval of 95%, power of 80% with a difference between outcome variable (major molecular remission) in the treatment groups of 0.4 [by assuming that 90% of participants on Imatinib and Artesunate will have major molecular remission vs 50% on Imatinib alone, a pooled proportion of 0.7 and attrition rate of 20%.[27] This gave a sample size of 25 participants per group. Therefore, 75 participants will be randomised into the three groups.

Inclusion and exclusion criteria

Inclusion criteria

Newly diagnosed, chronic-phase CML patients and patients with sub-optimal response to imatinib therapy who are 18 years and older will be recruited for the study.

Exclusion criteria

Patients with documented hypersensitivity to artesunate, patients with positive history of cardiovascular disease, renal or liver disease, hepatitis or retroviral infection, patients with positive pregnancy test or inability to give consent, and patients currently on any medication(s) that can interact with imatinib and/or artesunate will be excluded from the study.

Recruitment and procedures

Patients shall be recruited following the inclusion criteria at the study site. The study site is one of the two centres where CML patients in Nigeria are able to access Imatinib freely under the Glivec International Patient Assistance Program (GIPAP). Written informed consent will be obtained from each patient by the principal investigator before enrolment. Patients will then be assigned to their study arm based on the predetermined randomization order generated by the clinical trial randomization tool. Patient identification number will thereafter, be assigned to each patient which will serve as the patient identifier throughout the trial period and on the trial documents to ensure confidentiality of trial subjects.

Patients' biodata, disease history, current medications, and baseline parameters will be obtained following a prepared proforma. The study arms and interventions are summarized in Table 2. Blood samples for baseline tests will be collected, including full blood count (FBC), peripheral blood film (PBF), renal and liver function tests, hepatitis and retroviral screening tests, and BCR::ABL1 quantification and transcript type.

For Groups A and B, after each patient commences imatinib 400mg, 3mls of venous blood sample shall be collected through venipuncture into an Ethylene di-amine tetra acetic acid (EDTA) bottle at specified timepoints, this shall be centrifuged at 4000 revolutions/minute for 15 minutes to obtain plasma and stored at -20^{o}C until analysis (for imatinib-naïve pharmacokinetic analysis and drug level determination)

For Group C, 3mls of venous blood sample shall be collected through venipuncture into an EDTA bottle at specified timepoints. This will be further processed to obtain plasma and stored at -20^{o}C until analysis (baseline imatinib pharmacokinetic analysis and drug level determination). Patients in Group B and C will commence artesunate in addition to their imatinib medication 14 days before the next appointment day of follow-up.

A bio-analytical liquid chromatography-mass spectrometer (LC MS/MS) method of drug quantification analysis will be developed and validated according to ICH guidelines to simultaneously determine the amount of imatinib, its metabolite (N-desmethylimatinib) and

artesunate and its metabolite (dihydroartemisin). This method will be used to quantify the amount of these drugs in the plasma of the patients at baseline, 1-month, 3-months, 6-months and 12-months of follow-up. All laboratory tests and analysis shall follow the standard procedure.

Table 2: Study arms and interventions.

	Group A	Group B	Group C
CML status	Newly diagnosed	Newly diagnosed	Previously diagnosed
Interventions	Imatinib	Imatinib + Artesunate	Imatinib + Artesunate
Pharmacokinetic (PK) analysis	Imatinib naive (PK) + Steady state plasma levels	Imatinib naive (PK) + Steady state plasma levels	Steady state plasma levels

Table 3: Summary of schedules and activities.

	Activities	Study arm
Day 0,1	*Recruitment + Informed consent *Fill proforma (biodata, results of baseline laboratory tests) *Screen out patients with positive reaction to retroviral and hepatitis screening test *Document results of FBC, renal and liver function tests, BCR-ABL quantification * Patients commence Imatinib *Take blood samplings for baseline PK and drug level analysis	A, B, C
Day 7	Weekly phone call follow-up with patients	A, B, C
Day 15	Patients commence first cycle of artesunate Weekly phone call follow-up with patients	B, C
Day 21	Weekly phone call follow-up with patients	A, B, C
Day 29	End of first cycle of artesunate	B, C
Day 30 (1st month)	*First month clinic follow-up *Document results of FBC, renal and liver function tests *Take blood samplings for baseline PK and drug level analysis	A, B, C
Day 45	Patients commence second cycle of artesunate Scheduled phone call follow-up with patients	B, C
Day 59	End of second cycle of artesunate	B, C
Day 60 (2nd month)	*Second month clinic follow-up *Document results of FBC, renal and liver function tests	A, B, C
Day 75	Patients commence third cycle of artesunate Scheduled phone call follow-up with patients	B, C
Day 89	End of third cycle of artesunate	B, C
Day 90 (3rd month)	*Third month clinic follow-up *Document results for follow-up FBC, renal and liver function tests *Take blood samplings for baseline PK and drug level analysis *Group A and B are assessed for CHR and continue with the study in the absence of serious adverse event * Mutation screening for Group C *Sub-optimal patients (Group C) are assessed to decide if they are to continue in the study to 6 months milestone or taken off the study for escalated dose or second line therapy.	A, B, C
Day 105	Patients commence fourth cycle of artesunate Scheduled phone call follow-up with patients	B, C
Day 135	Patients commence fifth cycle of artesunate Scheduled phone call follow-up with patients	B, C
Day 165	Patients commence sixth cycle of artesunate Scheduled phone call follow-up with patients	B, C
Day 180 (6th month)	*Sixth month clinic follow-up *Document results of FBC, renal and liver function tests, BCR-ABL quantification *End of study for patients in Group C	A, B, C
Day 270 (9th month)	*Nineth month clinic follow-up	A, B
Day 360 (12th month)	*One year clinic follow-up	A, B

Table 4: Timeline for IMART trial.

S/N	Description of Activity	Duration	Year	Period					
				1	2	3	4	5	6
1.	Ethical approval	3 months	2025	√					
2.	Process development and validation of artesunate, SOPs development	3months	2025		√				
3.	Patients' enrolments	3-9 months	2025-2026		√	√			
4.	Clinical Trials, 1st year reports	15 months	2025-2026		√	√	√	√	√
5.	Data collation and analysis	3 months	2026				√	√	√
6.	Dissemination, Submission of results for journal publication and writing of final reports	6 months	2026				√	√	√

Follow-up

Patients will be followed up through regular weekly phone calls, patients will also go with a medication diary to document the time they take their medication(s) each day. Patients will then report to the clinic for the first month of follow-up, and the schedule continues as shown in Table 3. The proforma for data collection showing details of tests to be carried out is shown below.

Interventions

Imatinib mesylate from the innovator with the brand name Glivec will be used for the study as it is required to meet the recommended standards. Generic artesunate tablets each containing 50mg of artesunate, manufactured by Bond Chemical Industries Limited, Oyo State, Nigeria, will be used. This brand with batch no: 24001 has been analysed and has passed the quality assurance test as required by the International Pharmacopoeia (IP) concerning appearance, weight uniformity, hardness, disintegration, and chemical content of the API using a simple ultra-violet assay method.[28]

Side effect and adverse event reporting

Safety evaluations will be conducted at each of the patients' monthly follow-up visits. Adverse events may include any unwanted side effects, sensitivity reactions, abnormal renal or liver function test results, or other illnesses during the trial that may be expected or unexpected. The period for adverse event reporting will be from the time of first dose of the interventions in the study to the last clinic follow-up of the patient. Patients will be instructed to contact the principal investigator if there are any concerns or questions regarding their medication(s), and this will be handled on a case-by-case basis.

Patients on artesunate intervention (Groups B and C) with abnormal renal or liver function test that is significantly different from the baseline test results on recruitment will be closely monitored, while the primary physician/healthcare team will be consulted and the decision to take the patient off the study will be made as needed. Thus, the data monitoring committee will be a bi-monthly review between the research team and consultant haematologist in care of the patients.

Study assessment

The study procedure and laboratory tests to be carried out have been outlined in Table 3. Full blood count will be done using automated machines will be done using automated machines that provide accurate and reproducible results (Three Part Mindray BC 10 and Five Part Mindray BC 5000), liver function test, urea, creatinine and calcium levels will be done using Roche Cobas C311 autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany) using photometric method while sodium, potassium and chloride ions will be analysed with ion selective electrode (ISE), hepatitis and retroviral screening tests will be done using rapid diagnostic tests (RDTs) and BCR::ABL quantification will be done using Reverse Transcriptase Quantitative Polymerase Chain Reaction (RT-qPCR-TaqMan Chemistry) method; while the transcript variant will be performed using the Seeplex Leukaemia BCR::ABL1 transcript kit (Seegene, Seoul, Korea).

Patient compliance

Patients will be asked to bring their medications, packs and medication-time diary to each clinic follow-up. Compliance will be assessed by counting the remaining tablets at each follow-up visit and asking about compliance during weekly telephone follow-up. Compliance with other aspects of the trial protocol will also be assessed. Patients will be encouraged to report any concerns or side effects in a diary for review at each trial visit.

Patient and public involvement

Patients will be involved in the conduct and reporting of this study. They will be asked to keep a medication-time

diary and document any side effect(s) experienced. These will be reviewed during the weekly telephone follow-up and monthly clinic visits.

Study end points

The primary endpoint will be the achievement of Major Molecular remission (MMR/MR3) with BCR::ABL1 gene transcript ≤0.1 and deep molecular response (MR4) with BCR::ABL1 gene transcript ≤0.01 at 12 months. The secondary endpoints will include plasma imatinib levels at 6 and 12 months, disease progression, and adverse events relating to long-term use of artesunate.

Statistical analysis

The cumulative incidence of molecular response rate at 12 months, the primary end point, will be estimated using the Kaplan–Meier method. Secondary endpoints regarding patient characteristics and safety indices will be estimated with the use of paired-sample tests. Confidence intervals will be estimated at the 95% confidence level and 2-sided $p<0.05$ will be considered to indicate statistical significance.

A pharmacokinetic software, PKAnalix, a package of the Monolix Suite, will be used to analyse the plasma concentration-time data, to generate relevant pharmacokinetic parameters such as Cmax, AUC, half-life, and elimination rate constant. Analysis of variance or Kruskal-Wallis statistical tests would be used to analyse and compare the pharmacokinetic data across the three groups based on the normality of the data. Multiple imputation and pharmacometrics modelling will be used for extrapolations in cases of missing data despite rigorous follow-up.

DISCUSSION

The discovery and subsequent approval of Imatinib changed the status of CML from a terminal cancer to a manageable chronic condition. Despite this breakthrough, not all patients benefit from Imatinib. This may be a result of primary resistance, secondary resistance or suboptimal response to imatinib. Primary resistance manifests as failure of a newly diagnosed CML patient to achieve the treatment milestones as described by the European Leukaemia Net (ELN) guidelines, while secondary resistance is the loss of a previously achieved response to the drug due to the acquisition of new genetic mutations leading to loss of response to imatinib.[10] Imatinib resistance was as high as 24% after 18 months of follow-up in the global Phase III IRIS trial conducted across 16 countries in year 2010.[11]

Patients with resistance managed with Imatinib at standard dose will have suboptimal response to imatinib or treatment failure as described by the European Leukaemia Net (ELN) guidelines in Table 1.[10] These patients are usually managed by dose escalation of imatinib which is accompanied by increased risk of side-effects and only effective in cases of secondary resistance if resistance is due to overproduction of the target protein or low transporter activity. To ensure a favourable long-term outcome, patients are often placed on alternative TKI such as nilotinib, bosutinib or dasatinib.[29] In a resource-limited country like Nigeria where the first line TKI is only assessable to patients through the GIPAP Program, alternative TKIs are only available in very limited quantities if available at all.

Artesunate was found to significantly decrease the Ki65 biomarker for colorectal cancer (CRC) and improve clinical outcomes in a randomized, controlled, clinical trial where CRC patients used artesunate at a dose of 200mg daily for 14 days before surgery and standard care.[22] There is also evidence of artesunate anticancer efficacy in sunitinib-resistant renal cell carcinoma[15,] and artesunate was found to increase liver cancer cell sensitivity to sorafenib in advanced hepatocellular carcinoma.[14] In CML, artemisia extract (from which artesunate was derived), has been established to inhibit the activity of BCR::ABL1, which is implicated in over 90% of all CML cases.[18]

We hope that this study will be able to demonstrate a superior efficacy of Imatinib-artesunate combination over imatinib therapy alone in newly diagnosed chronic phase CML patients and improve clinical outcomes in suboptimal imatinib responders using the study endpoints described above. The study will also document the pharmacokinetics (PK) of Imatinib in the Nigerian CML patients and whether this PK is affected by co-administration with artesunate. The study may also establish the safety of artesunate when used outside its originally approved indication and for a prolonged period of time.

Strengths and limitations of this study

Randomization helps to remove bias in the study. Naïve sampling gives a clearer picture of the absorption phase of imatinib before accumulation starts while steady state gives information on the clearance and elimination phase of imatinib in these patients. Follow-up will be done immediately after each cycle of artesunate in Groups B and C which gives an avenue to document any adverse event early. The study is an initial pilot study (with 25 patients per study group), which may open an opportunity for a multicentre and multinational study.

CONCLUSION

The study, if positive, will provide a viable, assessable and efficacious CML therapy that reduces the incidence of imatinib resistance and an alternative to dose escalation or even TKI switch in cases of suboptimal response to imatinib, especially in resource-limited settings. However, further studies will need to be done to evaluate the long-term clinical outcome of the

combination therapy and evaluate the mechanism by which it produces its effect.

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