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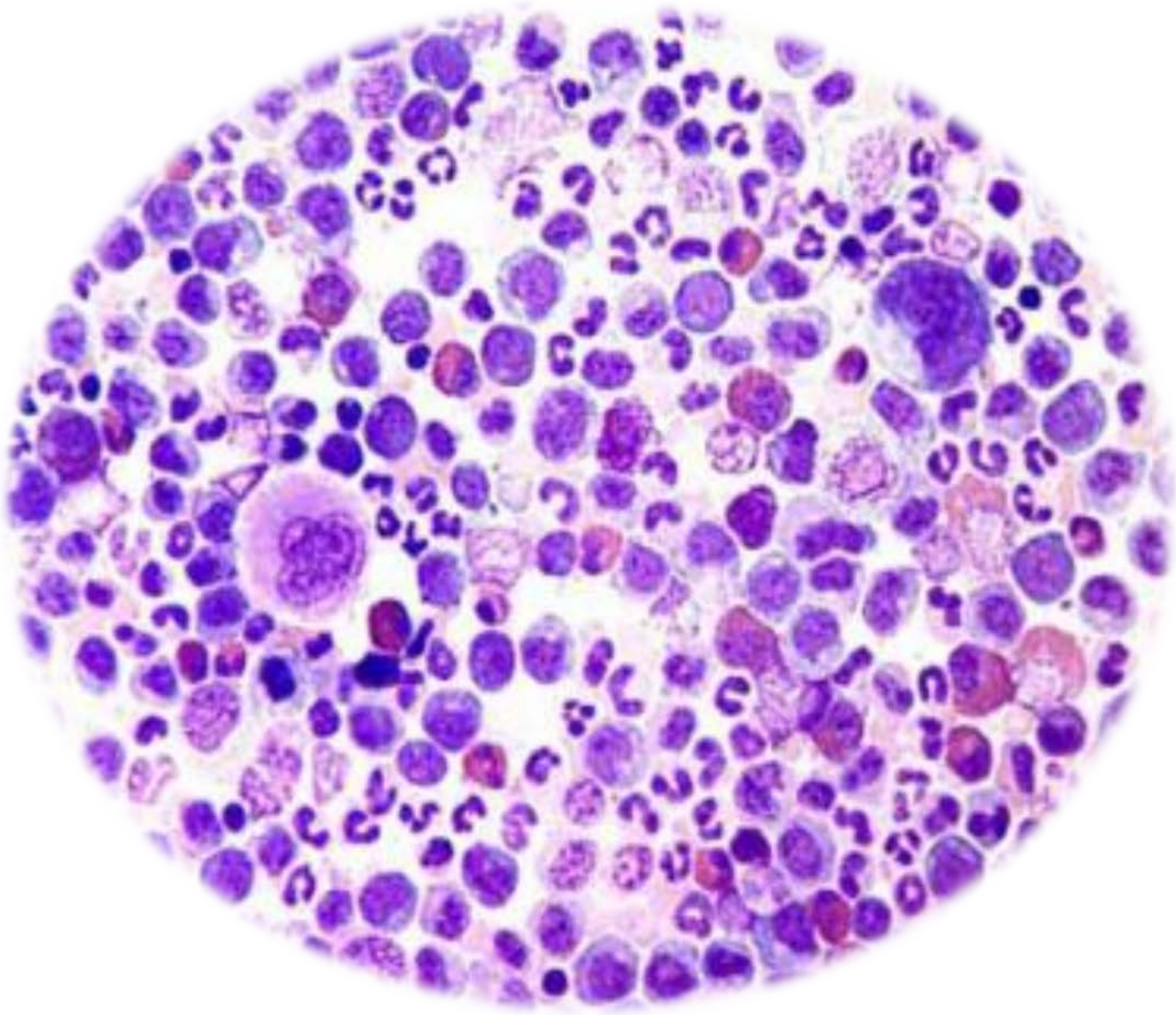

Chronic myeloid leukemia in a pediatric population in the Congo
Nitric Oxide (NO), Arylesterase (ARE) Paraoxanase (PON) and Renal Tumors

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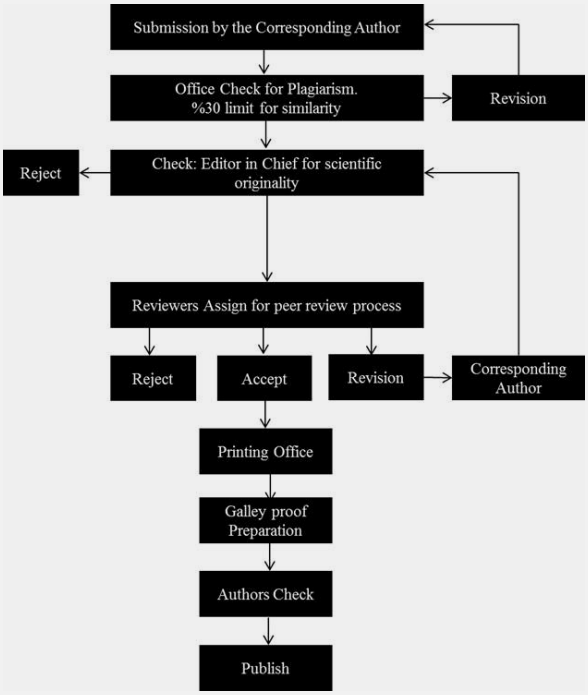

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Investigation of Serum Enzyme Activity of Nitric Oxide (NO), Arylesterase (ARE) and Paraoxanase (PON) in Renal Tumors

Tugba Gur[1]*, Gulsen Enterili[2], Necip Pirincci[3], Canan Demir[1], Halit Demir[2], Mehmet Kaba[3], Huseyin Eren[3]

Abstract

Objective: Reactive oxygen species (ROS) and antioxidant capacity have been implicated in the pathogenesis of various diseases, and cancers. Oxidative stress can cause tumor angiogenesis and may be carcinogenic. However, the relationship between antioxidant capacity and various cancers has been researched in several clinical trials.

Materials and Methods: In this study, we aimed to identify serum Nitric Oxide (NO), Arylesterase (ARE) and Paraoxonase (PON) activities in patients with renal tumors. Serum ARE, PON and NO levels were measured by spectrophotometer.

Results: Increased activity of serum Nitric oxide (NO) was determined in cancer group. Serum Arylesterase (ARE) were significantly lower in the patient group than the control group. Increased activity of Serum paraoxonase (PON) were detected in the control group ($p < 0.05$).

Conclusion: Our results indicates that Nitric oxide (NO), arylesterase (ARE) and paraoxonase (PON) activities may play an important role in the pathogenesis of renal cell cancer.

Keywords: Arylesterase, ARE, Nitric Oxide, NO, Serum paraoxonase, PON, Renal tumor

Introduction

Renal cell carcinoma accounts for 90–95% of all kidney malignancies (1). Advances in diagnostic imaging and early detection do not fully explain this trend rates of renal cancers are higher among males and have been increasing more rapidly among African Americans than Whites. In the United States, approximately 30,800 new cases of renal cancer and 12,000 deaths from renal cancer are reported annually, making renal cancer the sixth largest cause of cancer deaths. The incidence of renal cell carcinoma has been increasing in the United States and worldwide by approximately 2–4% per year, for the last 20 years (2,3).

Established risk factors for renal cancer include smoking, use of phenacetin containing drugs, hypertension, obesity, and end-stage renal disease (ESRD) (4). Metastatic kidney cancer is resistant to all ‘‘standard’’ forms of radiation therapy, chemotherapy, and hormonal therapies used in the treatment of other kinds of carcinomas.

Reactive oxygen species (ROS) have been implicated in the pathogenesis of various diseases, including cancers (5). In previous studies, it has been demonstrated that ROS are directly suggested in oxidative damage of cellular macromolecules such as lipids, proteins, and nucleic acids in tissues (6). Moreover, oxidative stress can lead to tumor angiogenesis. It has also been reported that ROS can also augment tumor cell migration, increasing the risk of invasion and metastasis (7).

However, the relationship between antioxidant capacity and various cancers has been investigated in several clinical trials. Ray et al. reported increased lipid peroxidation (LPO) and production of reactive oxygen metabolites (ROMs) and decreased activities of superoxide dismutase (SOD) in breast cancer patients. Increased glutathione peroxidase (GSHPx) activity also was reported by the same researchers (8). Vitamin E is a supporter of antioxidant system, and a supplementation trial conducted in China showed a significant reduction in stomach cancer mortality (9).

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Oberley and Buettner (10) reported that the vast majority of the cancer cells have very low SOD activity, as compared with their normal cell counterparts. Gecit et al. reported that increased prolidase seems to be associated with increased nitric oxide (NO) levels and oxidative stress along with decreased antioxidant levels in bladder cancer (11).

In this study, we aimed to identify serum Nitric Oxide (NO), Arylesterase (ARE) and paraoxonase (PON) activities in patients with renal tumors.

Material and Methods

A total of 32 male patients with renal cell cancer with a mean age of 55.32 +2.9 were included in the study. None of the patients smoked during their life, nor were they addicted to alcohol, and they did not use supportive antioxidants or any drug and they had no metabolic disorders. There were no other major diseases or cancers in any of the patients except for the kidney tumor. All the patients were newly diagnosed, and their blood samples were received in the preoperative period. In all, 29 male patients who made up the control group (mean age 56.01 + 3.0) were randomly selected among the volunteers who did not have any known major disease and did not use cigarettes, alcohol, drugs, and additional antioxidants. Patient and control groups had a similar socioeconomic status.

According to the results of radiological and postoperative histopathological evaluation, 24 (75%) of our patients were in stage 1, 6 (18.75%) of them were in stage 2, and 2 (6.25%) of them were in stage 4 of metastatic renal tumor.

The study protocol was carried out in accordance with the Helsinki Declaration as revised in 1989. All participants were informed about the study protocol and the written consent was taken from each one.

Blood collection

Following 12 h of fasting period, blood samples were taken in the morning, collected into empty tubes, and immediately kept on ice at 4 °C. The serum was then isolated from the cells by centrifugation at 5000 rpm for 10 min. Serum samples for measurement of Nitric Oxide (NO), Arylesterase (ARE) and paraoxonase (PON) levels were kept at -85 °C until they were used

Nitric Oxide (NO) analysis

NO levels in serum was determined using the Griess reaction (12). Griess solution X: 0.1 g NED (N-1-naphthyl)-ethylenediamine dihydrochloride) was weighed and dissolved in 100 ml water. Again, Y Griess solution: 1 g sulphanilamide in 100 ml of orthophosphoric acid (5%) was dissolved in a solution.

The 100 mico liter sample was taken and each tube was placed in a 0.1 ml Griess solution X and 0.1 ml Griess solution Y equal to tubes placed in and stirred, then 15 minutes at room temperature was allowed to stand and each sample at 540 nm absorbance values were read.

Arylesterase (ARE) analysis

Arylesterase activity in 2004 and 2005, developed by Erel was determined with a kit (13,14). 10 µml onto 990 ml diluent solution was added 10/100 ratio dilutions were performed this diluted from the 3 µml enrolled over 260 µml pure water (Reagent 1) was added, then 10 µml Reagent 2 was added, then vortexed and at 548 nm enzyme activity was measured.

Measurements are taken more spectrokuvet A1 80 µml Reagent 3 was added and again after waiting 4 minutes at 548 nm was measured and the measurements of activity is defined as A2. For activity measurement (enzyme unit) = (ΔA2-ΔA1) x1316.

Paraoxanase (PON) analysis

Paraoxonase activity in 2004 and 2005, developed by Erel was determined with a kit (13,14). The two tubes are each 500 µml reagent 1 (buffer solution) was added and on 25 µml sample (serum) was added and stirred then 25 µml reagent 2 (substrate solution) was added 30 sec and 150 sec after the absorbance measurement at 412 nm was read. Activity measurement (U/L) = ((Δ150sn-Δ30sn) / 2) x1202.84.

Statistical analysis

The defining statistics for the studied parameters were expressed in standard deviation. Student's t test was used for comparison of groups. In the study, 5% level was taken into account to the statistically significant differences between groups, and SPSS Statistical package program (ver. 13) was used for the all statistical computations.

Results

The demographic and clinical data of renal cancer and control groups are shown in Table 1. There were no statistically significant differences between renal cancer patients and controls with respect to age and body mass index (BMI) (all ps > 0.05; Table 1).

Serum NO level was significantly higher in renal cancer than in controls (all ps < 0.05); while ARE and PON levels were significantly lower ($p < 0.05$; Table 2). No correlation was observed between tumor staging and serum NO, ARE and PON levels (ps > 0.05).

Table 1: Demographic characteristics of the two groups in this study

Parameters	Control (n=32)	Patients (n=29)
Age, year	55.32 ± 2.9	56.01 ± 3.0
Body mass index, kg/m^2	21.56 ± 1.86	21.33 ± 1.29

Table 2: Descriptive statistics and comparison results according to the groups for specifications.

	Patients (n=32) (X±Sx)	Control (n=29) (X±Sx)	*p*
NO (µmol/L)	8.397± 2.0981	1.192± 0.1474	<0.001
ARE (U/mL)	17.518±3.5288	42.170± 6.8991	<0.001
PON (U/mL)	57.570±7.2911	94.423±4.7110	<0.001

Discussion

Biological and biochemical systems (CAT), peroxidase (POD), glutathione reductase (GSSG-Rx) and superoxide dismutase (SOD) are enzymes having antioxidant activity. Antioxidant defense system, cell free radical or other reactive molecules protects against oxidative damage. Therefore, this defense system, CAT, POD, PON, ARE, GSSG-Rx and antioxidant enzymes such as SOD is of great importance. The harmful effects of free radicals in cells are controlled by antioxidant defense systems (15).

Although some possible mechanisms through which oxidative stress exerts a regulatory role in tumor growth and progression including genomic instability (16), oncogene activation (17), and angiogenesis (18) are known, several important questions remain unanswered. It is not clearly known whether oxidative stres and tumor result from an increased oxidant production or from a failure of antioxidant systems (19). Although important changes in cellular redox homeostasis during tumor growth have been documented in experimental models, such variations have not been shown in humans.

Most of the difficulties encountered in these studies are related to the complexity of the biochemical pathways that regulate the cellular redox balance (19,20). A wide variety of oxidizing molecules such as ROS and/or depleting agents can change the glutathione redox state, which is normally maintained by the activity of GSH depleting (GSH-Px) and replenishing enzymes (glutathione reductase). The importance of GSH and related enzymes and their variation in tumors has been poorly studied (17,20).

Abnormal cell proliferation in the serum cancerous patient is the cause of lipid peroxidation (LP) increase. The increase in LP in cancer may also be owing to the poor antioxidant system as observed in the previous studies (21).

It has been claimed that MDA acts as a tumor promoter and cocarcinogenic agent on account of its high cytotoxicity and inhibitory action on protective enzymes (22, 23). The data reported in the literature on MDA levels in different human cancer types are controversial. On the other hand, MDA, the major aldehyde end product of LP of membrane polyunsaturated fatty acids by free radicals, is an indicator of oxidative stress (24). In the literature, NO level has increased in bladder cancer (11). In our study, NO levels were found to be higher in patients with renal cancer compared to controls ($p < 0.001$).

The data reported in the literature on oxidant, antioxidant molecule, and enzymes in different human cancer types are controversial. For instance, in a study the activities of SOD and GSH-Px enzymes were found lower in malignant liver tissues during rat hepatocarcinogenesis (25). In another one, Corrocher et al. (26) established that in human hepatoma the enzymatic antioxidant system was severely impaired owing to lowered GSH-Px activities. Nakada et al. (27) measured SOD activities in renal cell carcinoma and non tumorous renal tissues. They found no meaningful differences between the activities of the cancerous and noncancerous parts and suggested that it was unlikely for SOD to play a part in the development of renal cell carcinoma since SOD activities in tumor tissue were similar to those in nontumorous renal tissues. Ray et al. (8) observed a significant increase in SOD and GSH-Px activities in patients with gastric cancer compared to the control group. Ozturk et al. (28) observed a significant increase in xanthine oxidase (XO) activity in patients with cancerous human colorectal tissues compared to control group. The increased GSH-Px activities and GSH levels are reported in patients with leukemia (29, 30). In our study group, serum ARE was significantly lower than the control group ($p < 0.001$). In that study, results indicated that there was a significant difference in serum PON activtys between patient and control groups ($p < 0.001$).

Conclusions

Oxidant/antioxidant balance of damage in the development kidney cancer might be considered a risk factor. Our results indicate that Nitric oxide (NO), arylesterase (ARE) and paraoxonase (PON) activities play an important role in the pathogenesis of renal cell cancer.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was conducted due to defined rules by the Local Ethics Commission guidelines and audits.

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Chronic myeloid leukemia in a pediatric population in the Congo

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Abstract

Objective: Chronic myeloid leukemia is a rare hematological malignant disorder among children and adolescents for which data are scare in Africa. The aim of the study is to report clinical, biological feature of children with chronic myeloid leukemia. Additionally, describing cytogenetic response to imatinib and adherence of children to the drug.

Patients and Methods: A retrospective study was carried out from January 2007 to December 2016 (10 years) in the department of Hematology at the Teaching Hospital in Brazzaville. Four of 52 patients admitted during the period for chronic myeloid leukemia, were children. We collected data from these children's medical records for analysis.

Results: They were four adolescents (2 boys and 2 girls) with a median age of 13.75 years at the time of diagnosis (range 11.2 and 16 years) that presented at the chronic phase of the the chronic myeloid leukemia. Delay diagnosis was 4 months. All adolescents presented with a voluminous splenomegaly (median size: 16.75 cm) and high white blood cells count: 133.37G/L (range: 60.7 and 219 G/L). The response to imatinib was poor. None patient was adherent to the treatment.

Conclusion: Chronic myeloid leukemia in children in the Congo is rare. Abdominal pain and voluminous splenomegaly are the main finding symptoms of the malignancy. Despite the delayed diagnosis of the disease, children present at chronic phase. The response to imatinib is poor as children are not adherent to the treatment.

Keywords: Chronic myeloid leukemia, children, Congo

Introduction

Chronic myeloid leukemia (CML) is a positive Philadelphia chromosome clonal myeloproliferative disorder that affects mostly in adulthood. It is rare among children and accounts for 2-3 % of all childhood leukemia (1). Even though CML pediatric and adult population share the same fusion gene BCR-ABL, Krumbholz, et al have shown that breakpoint distribution in BCR in children is different than adult (2). Besides pediatric CML compared to adult one is described as more aggressive (3). Imatinib is, as in adults, an effective first line treatment in children and adolescents with CML (1). It has showed impressive complete cytogenetic response rates (1). In our knowledge only one study has described specifically the CML pattern in pediatrics population in Sub Saharan Africa (4). We are complementing it by describing the clinical, biological pattern of CML in children as well their response and adherence to imatinib.

Patients and Methods

The retrospective study took in the Hematology department at the teaching hospital, largest hospital in the country from January 2007 to December 2016 (10 years). All medical records of patients younger than 18 years at the enrollment who had chronic myeloid leukemia were enrolled in the study. For each patient, we collected demographic, clinical and biological data. The hematological and cytogenetic responses to imatinib were analyzed with regard to the European Leukemia Net Guidelines and U.S National Comprehensive Cancer Network (NCCN) Guidelines (5).

Adherence to imatinib was assessed by counting the number of days of imatinib taken. Patients were defined as non adherent when there were discontinuing their treatment for at least ninety days.

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Statistical analysis: For the description of each quantitative variable, median, range, frequencies and percentages were calculated.

Results

Clinical and biological characteristics are shown in the table 1. Four children (7.69%) on 55 patients with chronic myeloid leukemia were included in the study. They were two males and two girls with an average age of 13.75 years (range 11.6 and 16.3 years). The delay diagnosis was 4 months (range 1 and 6 months). Abdominal pain was the most common symptoms. All patients presented a splenomegaly with a median size of 16.75 cm (range 14 and 19 cm).

Initial cell blood counts accounted for an average leukocytosis at 133.37 G/L (range 60.7 and 219 G/L). At the differential, blast accounted in average for 2.3% (range 1 and 5%).

The average hemoglobin rate was 7. 45 g/dL (range 7.9 and 11.3g /dL) and platelets 435.25G/L (range 359-480 G/L).

All patients presented at the chronic phase.

Imatinib was initiated at 400 mg daily for all patients. The median time to achieve a complete hematological response was 8 weeks (4 and 9.5 weeks). All patients were not adherent to imatinib. They discontinued their treatment on themselves without the agreement of their medical providers. The average duration of the discontinuation was 98 non cumulative days (range 90 and 128 days).

At 6 months three patients (75%) showed minor cytogenetic responses and one (25%) did not respond to the treatment.

Table 1: Clinical and biological characteristics of CML children (+ : present, - : absent)

	Patient N°1	Patient N°2	Patient N°3	Patient N°4
Gender	M	F	M	F
Age in year	11.6	13.2	14 ans	16.3
Delay delay diagnosis in month	1	5	4 mois	6
Symptoms				
Fever	-	-	-	-
Fatigue	+	+	+	-
Lost of weight	-	+	+	+
Abdominal pain	+	+	+	+
Splenomegaly size in cm	14	19	15	19
Blood count (G/L)				
GB	83,8	219	60,7	170
Hb	11,3	7,9	8.3	10.8
Plaquettes	429	480	359	473
Blast (%)	1	5	1	2.3
Phase of CML	Chronic	Chronic	Chronic	chronic

Discussion

Pattern of CML in the African continent have been broadly reported, however most of them were focused on the adult population. CML in children remain unexplored (4). Few reports in the region have been published. To our knowledge, no one of them debates the topic of adherence to the treatment (4,6). CML is also in the African continent a rare blood disorder in the childhood. In the Hematology department in Brazzaville, which is the unique department that manages hematological malignancies in the country, it constitutes 7.69% on a cohort of 52 patients. In Senegal CML in children accounts for 11% in and 1.2% in eastern India (4,7).

It appears that preteens and teenagers are more affected by CML in the pediatric population with an average age that ranges from 11.5 to 16 years (4,6,7). Children from low and middles resources countries are older at the time of the diagnosis due to the long delay diagnosis of the CML (8,9). Consequent to the tardy diagnosis, children present with abdominal pain and voluminous splenomegaly that can confuse physicians to tropical splenomegaly in our region. They also have elevated white blood cell (WBC) counts. Fall et al showed an average count of 244G/L of WBC and a moderate anemia (4). Thrombocytosis is rare in children (3). Despite delayed diagnosis of the CML, children as well as adults in our cohort present at the hospital at chronic phase of the disease (8).

Cytogenetic responses monitored at 6 months of treatment showed poor performance of imatinib in our series since none complete cytogenetic responses (CCR) were noticed. El-Affy, Fall and Rault et al reported respectively 53, 55 and 75% of complete cytogenetic responses (4,6,7). Nonetheless, we should be cautious while comparing these rates. Indeed when we peruse the results of Rault et al, we can read that at 6 months of the treatment, the CCR was monitored only on 4 patients over 9 and sole one patient (25%) showed a CCR (7). Opimal response to imatinib is lower in the pediatric when we compare with adults (4). Poor adherence of children mainly adolescent is usually reported as cause of this low performance (10).

Conclusion

Chronic myeloid leukemia in children is a rare in the Congo. It shares clinical and biological feature with adults. However, the lower performance of the imatinib in this population related in some part to the poor adherence of the treatment, request specific interventions and management by the medical team.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was conducted due to defined rules by the Local Ethics Commission guidelines and audits.

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