

# Successful Nilotinib Treatment in a Child with Chronic Myeloid Leukemia

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## Key Words

Chronic myeloid leukemia · Nilotinib · Off-label drug use · Tyrosine kinase inhibitor

## Abstract

A 16-year-old female was diagnosed incidentally with chronic myeloid leukemia (CML) in the chronic phase. She showed complete remission after 3 months of nilotinib treatment. CML is a rare malignant neoplasm in pediatric age. It is characterized by a Philadelphia chromosome, which comes from a genetic translocation between chromosomes 9 and 22. This translocation results in an abnormal fusion called BCR-ABL oncogene which encodes a chimeric BCR-ABL protein. This protein is the underlying cause of CML. Nilotinib is a newly licensed drug for CML in adults. Structurally, it is similar to imatinib (the older tyrosine kinase inhibitor), but it is much more potent in inhibiting BCR-ABL due to its much increased affinity for its binding site. Specific guidelines for CML treatment in children have yet to be determined. In our patient, nilotinib was used as an off-label drug because it is not licensed for children. According to the pharmacokinetic response to drugs, children cannot be considered small adults irrespective of their weight. Off-label drug use based on evidence that it is the best treatment available is an important tool in the hands of expert treating physicians.

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## Introduction

Children are defined as individuals aged 0–18 years. In pediatrics, the patient may be a premature infant weighing 500 g or a fully grown adolescent weighing as much as 100 kg.

Doses for children are often derived by scaling from adult dosages after adjusting for body weight. However, it is well known that pharmacokinetic responses to a drug, such as drug absorption, distribution, metabolism, and excretion, are substantially different in children as compared with adults [1]. Chronic myeloid leukemia (CML) is a chronic clonal myeloproliferative neoplasm originating in a pluripotent stem cell common to all three hematopoietic lineages, characterized by overproduction of myeloid cells in all stages of maturation. It is the first malignant disease to be associated with a genetic lesion and the first leukemia to provide a genotype model conducive to targeted molecular therapy [2]. CML accounts for 20% of adult leukemias and its incidence is approximately 1–2 per 100,000 population per year. It is more common in men than in women, with a 2:1 ratio. Generally, older people are affected by the disease, with a median age at diagnosis of around 65 years [3]. Fewer than 10% of CML patients are younger than 20 years [4]. CML is characterized by a genetic translocation between chromosomes 9 and 22, the new chromosome called Philadelphia chromosome (Ph); its karyotype t(9;22). The translocation results in an abnormal fusion called BCR-ABL oncogene, which encodes a chimeric BCR-ABL protein that has constitutively activated ABL tyrosine kinase activity; this protein is the underlying cause of CML [5]. BCR-ABL protein activates a cascade of proteins that control the cell cycle, speeding up cell division and inhibiting cell apoptosis. Moreover, the BCR-ABL protein inhibits DNA repair, causing genomic instability and making the cell more susceptible to developing further genetic abnormalities [6]. The identification of this protein has made it an ideal target for therapeutic intervention [7]. Most patients (60%) are diagnosed in the initial chronic phase (CP) of the disease, in which patients experience night sweats, general malaise, diminished appetite, fatigue, and breathlessness. The remaining 40% of patients are asymptomatic and identified by a routine blood test [8]. Imatinib is a tyrosine kinase inhibitor (TKI), which is the approved treatment for CML in the pediatric age, but we used nilotinib, the second-generation TKI, as off-label drug use (OLDU), based on evidence that it is more effective than imatinib. OLDU refers to drug use for unlicensed indications that are beyond the specifications authorized for marketing, whether in terms of doses, preparation, patient population, or route of administration [9].

### Case Study

A 16-year-old Kuwaiti female presented to the emergency clinic with a common cold. Her weight was 86 kg. The routine investigations showed high white blood cell (WBC) count, mainly neutrophils. She was treated with paracetamol 1,000 mg three times daily to follow up with her general practitioner, but she did not attend any follow-up. After 1 year she presented again to the emergency clinic with a common cold. A complete blood count (CBC) showed a much higher WBC count with a very high neutrophil count: WBC 88.6 ( $4\text{--}10 \times 10^9/\text{l}$ ), red blood cells (RBC) 6.00 ( $3.8\text{--}4.8 \times 10^{12}/\text{l}$ ), hemoglobin (Hb) 114 g/l (120–150), hematocrit 0.372 L/L (0.36–0.46), mean corpuscular volume 62 fl (83–101), mean corpuscular hemoglobin 19 pg (27–32), mean cell hemoglobin concentration 305 g/l (315–345), red cell distribution width (RDW) 19.3 (11.6–14%), platelet count 187 ( $150\text{--}410 \times 10^9/\text{l}$ ), mean platelet volume 10.2 fl (7–11), neutrophils 89.8 (40–80%), lymphocytes 6.8 (20–40%), monocytes 3.2 (2–10%), eosinophils 0.2 (1–6%), and basophils 0.0 (<1–2%). The glucose, the serum ferritin and the coagulation profile were normal through the course of her treatment. High-performance liquid chromatography result was Hb A: 96.67 (96–98%), Hb F: <1% (<1%), and Hb A2: 2.45 (1.5–3.5%), which showed a normal pattern. However, based on her normal serum ferritin and hypochromic microcytic picture, she was most likely to

have an alpha thalassemia trait, but no globin gene analysis was done. The abdominal ultrasound study was normal. Bone marrow aspiration confirmed a diagnosis of CML by cytogenetic, fluorescence in situ hybridization (FISH), and real-time quantitative polymerase chain reaction (RT-Q-PCR) methods. Nilotinib treatment was started at a dose of 150 mg with 2 tablets twice daily. After 1 month, only the nilotinib dose of 200 mg was available, so she switched to a dose of 400 mg in the morning and 200 mg at night time. She showed liver enzyme derangements after 1 month on nilotinib. The dose was reduced to 200 mg twice daily until the liver enzyme improved. After 1 month, she switched again to 400 mg in the morning time and 200 mg at night time. The CBC and the biochemistry profile for the course of her treatment shown in [table 1](#). After 30 days, she showed a reduction from 30 to 8.3% on RT-Q-PCR. After 90 days she achieved major molecular remission ([table 2](#)).

## Discussion

Children and young adults are only a small percentage of patients diagnosed with CML, which represents about 3% of newly diagnosed childhood leukemias. CML has the same disease course in children as it does in adults. The features of the disease at diagnosis and the response to therapy in children seem to be identical to that in adults. Specific guidelines for CML treatment in children have yet to be determined [10].

Diagnosis of CML is carried out by several procedures as conventional cytogenetic testing after culturing the bone marrow sample to detect the Ph chromosome which is caused by translocation between chromosomes 9 and 22. FISH is another way to look at chromosomes. FISH can be used to look for the specific pieces of the BCR-ABL gene and it can be used on regular blood or bone marrow samples without culturing the cells first [11]. PCR method is a super-sensitive test that can be used to look for the BCR-ABL oncogene in leukemia cells. It can be done on peripheral blood or bone marrow samples and it can detect very small amounts of BCR-ABL, even when the Ph could not be detected in bone marrow cells with cytogenetic testing [12]. The monitoring of BCR-ABL transcript levels by RT-Q-PCR has become important to assess minimal residual disease and standard of care in the treatment of CML. Three-month monitoring using Q-PCR may provide the prognostic data needed for a treatment decision [13].

Historically, CML was treated with conventional busulfan or hydroxyurea and associated with a poor prognosis. The development of imatinib TKI targeted against the causative BCR-ABL oncoprotein has resulted in hematologic and cytogenetic remissions in all CML phases. A significant number of patients are resistant to imatinib or develop resistance during treatment. This is often a result of mutated forms of the BCR-ABL oncoprotein to which imatinib is unable to bind. Several strategies have been developed to overcome the problem of imatinib resistance, including high-dose imatinib [14].

Nilotinib is an orally highly selective TKI, which is structurally similar to imatinib but much more potent in inhibiting BCR-ABL due to its much increased affinity for its binding site creating greater specificity. It is effective against wild-type and many imatinib-resistant BCR-ABL1 mutations. Trials showed that Nilotinib is superior to imatinib in terms of cytogenetic and molecular remission and rates of disease progression in newly diagnosed patients. It has therefore been approved as first-line therapy for adult patients with CML in the CP by the Food and Drug Administration [15]. The most common side effects with nilotinib are thrombopenia, neutropenia, anemia, headache, nausea, constipation, diarrhea, rash, pruritus, fatigue and higher rates of dermatologic toxicity and biochemical abnormalities associated

with hepatic and pancreatic toxicity compared with imatinib, but lower rates of edema, gastrointestinal symptoms, muscle spasm, and neutropenia [16].

Complete cytogenetic remission criteria included morphologically normal bone marrow with complete disappearance of Ph positive in at least 20 metaphases examined. Cytogenetic relapse was defined by the detection of one or more Ph positive marrow metaphases and confirmed by a subsequent cytogenetic study. Complete cytogenetic remission was considered durable if it lasted for at least 6 months [17].

Complete molecular remission was achieved if the BCR-ABL/BCR ratios showed a reduction to 0.1% ( $\leq 3$  log) from a standardized baseline according to the international scale and if this was confirmed in two subsequent samples [18].

Drugs in OLDU for children can be prescribed in a different dose, for a different indication, or by a different route of administration than what the drug is licensed for [19]. In the United States, OLDU implies the prescription of a drug that is not specified in the labeling approved by the US Food and Drug Administration [20]. As such, the term 'off-label' does not imply an improper, illegal, contraindicated, or investigational use. Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient [21].

## Conclusion

We have to be careful because according to the pharmacokinetic response to drugs, children cannot be considered small adults irrespective of their weight. OLDU based on evidence as the best treatment available is an important tool in the hand of the expert physician. Nilotinib showed both complete cytogenetic and major molecular remissions in our patient with only transient adverse effects. More research trails should be encouraged to approve its use in pediatric age.

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## Disclosure Statement

H.A.J. is serving as a Consultant Haematologist at Amiri Hospital in Kuwait. There are no conflicts of interest for any of the authors.

## References

- 1 Kimland E, Odland V: Off-label drug use in pediatric patients. *Clin Pharmacol Ther* 2012;91:796–801.
- 2 Pavón V, Gómez R, Jaime JC, Hernández P, Arencibia A, Espinosa-Martínez E, Ávila OM, Hernández C, González A, Carnot J, Espinosa-Estrada E, Lam RM, Amor AM, Lavauth K, Hernández A: Introduction of imatinib as first-line therapy for chronic myeloid leukemia in Cuba. *MEDICC Rev* 2011;13:35–40.
- 3 Camgoz A, Gencer EB, Ural AU, Baran Y: Mechanisms responsible for nilotinib resistance in human chronic myeloid leukemia cells and reversal of resistance. *Leuk Lymphoma* 2013;54:1279–1287.

- 4 Horvath A, Baghiu MD, Pap Z, Banescu C, Marginean CO, Pavai Z: Follow-up of childhood chronic myelogenous leukemia with monitoring the BCR-ABL fusion gene expression in peripheral blood. *Rom J Morphol Embryol* 2011;52:907–913.
- 5 Weisberg E, Manley WP, Cowan-Jacob SW, Hochhaus A, Griffin JD: Second generation inhibitors of BCR-ABL for the treatment of imatinib-resistant chronic myeloid leukaemia. *Nat Rev Cancer* 2007;7:345–356.
- 6 Mondal JD, Tewary D, Sardar SM: Chronic myeloid leukemia – an overview. *Int J Sci Res* 2014;3:128–132.
- 7 Bauer S, Romvari E: Treatment of chronic myeloid leukemia following imatinib resistance: a nursing guide to second-line treatment options. *Clin J Oncol Nurs* 2009;13:523–534.
- 8 Simoneau CA: Treating chronic myeloid leukemia: improving management through understanding of the patient experience. *Clin J Oncol Nurs* 2013;17:E13–E20.
- 9 Andolina JR, Neudorf SM, Corey SJ: How I treat childhood CML. *Blood* 2012;119:1821–1830.
- 10 Walter J: Chronic Myeloid Leukemia. *The Leukemia and Lymphoma Society* 2012, pp1–44.
- 11 Pajor G, Kajtar B, Pajor L, Alpar D: State-of-the-art FISHing: automated analysis of cytogenetic aberrations in interphase nuclei. *Cytometry A* 2012;81A:649–663.
- 12 Soverini S, Hochhaus A, Nicolini FE, Gruber F, Lange T, Saglio G, Pane F, Müller MC, Ernst T, Rosti G, Porkka K, Baccarani M, Cross NCP, Martinelli G: BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European Leukemia Net. *Blood* 2011;118.
- 13 Associação Brasileira de Hematologia E Hemoterapia; Sociedade Brasileira de Patologia; Sociedade Brasileira de Pediatria: Chronic myeloid leukemia (in Portuguese). *Rev Assoc Med Bras* 2013;59:220–232.
- 14 Jabbour E, Cortes JE, Giles FJ, O'Brien S, Kantarjian HM: Current and emerging treatment options in chronic myeloid leukemia. *Cancer* 2007;109:2171–2181.
- 15 Mealing S, Barcena L, Hawkins N, Clark J, Eaton V, Hirji I, Davis C: The relative efficacy of imatinib, dasatinib and nilotinib for newly diagnosed chronic myeloidleukemia: a systematic review and network meta-analysis. *Exp Hematol Oncol* 2013;2:5
- 16 Wei G, Rafiyath S, Liu D: First-line treatment for chronic myeloid leukemia: dasatinib, nilotinib, or imatinib. *J Hematol Oncol* 2010;3:47.
- 17 Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, Gathmann I, Bolton AE, van Hoomissen IC, Goldman JM, Radich JP: Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2003;349:1423–1432.
- 18 Serpa M, Sanabani SS, Dorliac-Llacer PE, Conchon M, Meneguim Pereira TD, Nardinelli L, Costa JL, Yoshinaga Novaes MM, de Barros Ferreira P, Bendit I: Molecular measurement of BCR-ABL transcript variations in chronic myeloid leukemia patients in cytogenetic remission. *BMC Blood Disord* 2010;10:7.
- 19 Langerová P, Vrtal J, Urbánek K: Incidence of unlicensed and off-label prescription in children. *Ital J Pediatr* 2014;40:12.
- 20 Thomadsen BR, Thompson Heaton II H, Jani SK, Masten JP, Napolitano ME, Ouhib Z, Reft CS, Rivard MJ, Robin TT, Subramanian M, Suleiman OH: Off-label use of medical products in radiation therapy: summary of the report of AAPM Task Group No. 121. *Med Phys* 2010; 37:2300–2311.
- 21 Neville KA: Off-label use of drugs in children. *Pediatrics* 2014;133:563–567.

**Table 1.** Blood tests for CBC and liver function tests during nilotinib treatment

Investigation intervals	WBC	RBC	Hb	MCV	MCH	Plate	Net	Lymp	Mom	ALT	AST	GGT
One year before	38.8	5.82	113	62	19	293	83.5	11.8	4.0	NA	NA	NA
On presentation	88.6	6.00	114	62	19	187	89.8	6.8	3.2	26	25	NA
Day 30	9.7	4.6	88	63	19	195	77	19	2	86	65	134
Day 90	11.7	4.7	104	58	18	173	35	58.1	6.4	42	31	46
Day 210	15.4	5.5	101	58	18	180	72	20.9	4.6	22	21	42
Day 300	17.6	6.05	107	60	18	297	58	24	7	19	18	36
Day 390	17.5	6.28	108	57	17	204	72	19.2	7.0	21	20	27

MCV = Mean corpuscular volume; MCH = mean corpuscular Hb; Plate = platelet; Net = neutrophils; Lymp = lymphocytes; Mon = monocytes; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma glutamyl transferase.

**Table 2.** Nilotinib effect on cytogenetic and molecular levels

Treatment intervals	Sample	Cytogenetic karyotype (morphological)	FISH LSI BCR/ABL	Molecular RT-Q-PCR BCR-ABL/BCR	Remission status
On presentation	BM	46,xx,t(9:22)	90%	30%	No CCyR or MMR
Day 30 on nilotinib	PB	ND	ND	8.6%	No MMR
Day 90 on nilotinib	PB	ND	ND	0.032%	MMR
Day 210 on nilotinib	PB	ND	ND	0.0056%	MMR
Day 300 on nilotinib	PB	ND	ND	0.0092%	MMR
Day 390 on nilotinib	PB	ND	ND	0.0072%	MMR

LSI = Locus-specific identifier; CCyR = complete cytogenetic remission; MMR = complete molecular remission; ND = not done; BM = bone marrow; PB = peripheral blood.