Case report

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Case report: Efficacy of ponatinib in a case of chronic myeloid leukemia with a complicated clonal evolution including a myelodysplastic syndrome

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Abstract

Chronic myeloid leukemia (CML) is characterised by the presence of the Philadelphia chromosome (Ph), which results in the production of the constitutively active tyrosine kinase BCR-ABL1, with tyrosine kinase inhibitors (TKI) targeted against this protein now being the mainstay of therapy. Clonal evolution in Ph-positive cells is rather uncommon in the chronic phase of CML (CP-CML) but is associated with disease progression, and although chromosomal abnormalities in Ph-negative cells have been described during imatinib therapy and more recently with newer TKIs, albeit rarely, clinical consequences remain unclear. Some of these patients do however evolve to a myelodysplastic syndrome (MDS) or an acute myeloid leukemia (AML), with loss of chromosome 7 seeming to confer the highest risk.

The case is that of a patient with CP-CML diagnosed in 2008 who initially experienced secondary resistance to imatinib, with the G250E and E459K point mutations in the BCR-ABL1 kinase domain (KD) being detected. Secondary resistance to dasatinib later developed, and this time the F317L BCR-ABL1 KD mutation was detected. Furthermore, a MDS with features of poor prognosis including loss of chromosome 7 in Ph-negative cells was diagnosed in 2012 while she was demonstrating a deep molecular response of her CML on nilotinib therapy. Azacitidine was added and resulted in a response of the MDS with a transfusion independency. The -7 clone was never again detected, but a gain of chromosome 8 (+8) was found on subsequent cytogenetic studies, as well as a sub-clone of Ph-positive cells harboring a t(5;20) (q32;q13) translocation. Due to loss of molecular and cytogenetic responses of her CML on nilotinib, the patient was switched to ponatinib and azacitidine was stopped. This resulted in a sustained major molecular response of her CML at 24 months, with no signs of recurrence of the MDS. Interestingly, the +8 clone has persisted on two cytogenetic studies performed after initiating ponatinib.

This report raises important issues regarding the natural history of CML and to the significance of seemingly independent Ph-negative clones identified during TKI therapy, as well as suggesting the efficacy of ponatinib in the presence of complicated clonal and mutational evolution of the Ph-positive cells as well as a MDS.

Keywords: Chronic myeloid leukemia, ponatinib, loss of chromosome 7, gain of chromosome 8, secondary myelodysplastic syndrome, clonal evolution, CML, chromosomal cytogenetic abnormalities, monosomy 7, trisomy 8

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by dysregulated clonal proliferation of mainly myeloid but also erythroid cells and platelets. The

Philadelphia chromosome (Ph), resulting from the t(9;22) (q34;q11) reciprocal translocation, is characteristic of the disease and results in the production of the dysregulated tyrosine kinase BCR-ABL1, at the heart of the pathogenesis of CML [1].

CML historically progressed from a rather indolent chronic phase (CP-CML) to an accelerated phase where the disease is harder to control and generally culminating in an acute leukemia or blast crisis (BC-CML), although this is rare since the introduction of tyrosine kinase inhibitors (TKI) directed against BCR-ABL1.

TKIs are now the mainstay of therapy for CP-CML, with imatinib, dasatinib and nilotinib representing first-line treatment options for such patients [2]. Different mechanisms can contribute to TKI resistance, with point mutations in the *BCR-ABL1* kinase domain (KD) being a well described mechanism of acquired resistance to imatinib [3,4]. Ponatinib is a new TKI that has shown activity against CP-CML resistant to first and second-generation TKIs due to *BCR-ABL1* KD mutations and is the only currently available TKI active against the T315I mutation [5-7].

Monitoring response to TKI therapy has historically been done using various methods, with quantitative real time polymerase chain reaction (qRT-PCR) measurement of BCR-ABL1 transcript level on the international scale (IS) now being used to monitor molecular response to treatment [2,8]. Nonetheless, fluorescence *in situ* hybridization (FISH) and conventional cytogenetic studies on bone marrow specimens are still recommended at diagnosis, with the latter remaining of great value in cases of treatment failure to identify possible evolution of the CML clone or clonal chromosomal abnormalities (CCAs) in Ph-negative cells [2,9]. *BCR-ABL1* mutational analyses are also recommended in cases of treatment failure [2]. Recurrent molecular mutations involving other genes than *BCR-ABL1*, such as *ASXL1*, *RUNX1*, and *TET2*, amongst others, seem to be common in BC-CML patients but have also been identified in a small proportion of CP-CML patients with unclear prognostic implications, and data is currently lacking to recommend searching for such mutations [10,11].

CCAs in Ph-positive cells is identified in 5% of CP-CML patients but is present in 50-80% of BC-CML cases [12]. They are a feature defining treatment failure or an accelerated phase of CML [2,13]. They are thought to reflect the genetic instability of the CML progenitors, conferred at least partly by the BCR-ABL1 protein [14-16]. Clonal evolution of Ph-positive cells can therefore manifest itself as CCAs in addition to the Ph chromosome, point mutations in *BCR-ABL1* (usually in the KD) or mutations in other genes.

CCAs in Ph-negative cells arising during treatment for CML are rare and were initially described in patients exposed to chemotherapy and interferon- α but are increasingly reported in patients treated with imatinib, and more recently dasatinib and nilotinib, with cases now reported in patients treatment naive before the use of TKIs [17-21]. These anomalies have unclear clinical implications, with only a minority of patients eventually developing a secondary hematological neoplasm such as a myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML) [18,21-23]. Loss of chromosome 7 (-7) seems to confer the highest risk for secondary MDS/AML, based on

case series and anecdotal reviews [23]. In a literature review by Groves and al in 2011, 16 of 53 patients with TKI-treated CML in whom -7 or del(7q) was identified developed a MDS/AML, with -7 present in all cases [19]. The latest European Leukemia Net recommendations on the management of CML consider -7 or del(7q) in Ph-negative cells as a warning sign requiring more frequent monitoring [2].

Myelodysplastic syndromes form a heterogeneous group of clonal malignant neoplasms that have a variable risk of progression to AML and are characterized by dysplastic and ineffective hematopoiesis. This results in peripheral blood cytopenias with expected clinical consequences and dysplastic changes on bone marrow examination [24]. They can arise following cytotoxic chemotherapy given for another neoplasm and, as mentioned, have been described in a few cases of patients receiving TKI therapy for CML. Progression of CML in such patients must however be excluded. MDS treatment varies according to risk stratification on the revised International Prognostic Scoring System (R-IPSS) risk score, which incorporates the karyotype and patient characteristics [25]. Options include supporting care such as transfusions and growth factors, active treatment with hypomethylating agents such as azacitidine or decitabine to stabilize and modify the course of the disease, with allogeneic hematopoietic stem cell transplantation (alloSCT) being a potentially curative option available to a minority of patients [26].

Case presentation

The patient presented with asthenia and abdominal pain in September 2008 at 58 years old. A complete blood count revealed leucocytosis at $669 \times 10^9/L$ with 3% myeloblasts on immunophenotyping, anemia at 84 g/L and a platelet count of $355 \times 10^9/L$. She was not known for any other prior medical condition. The Philadelphia chromosome as well as a typical e14a2 BCR-ABL1 transcript subtype were identified and she was therefore diagnosed with CP-CML. Unfortunately, the original bone marrow aspirate was inadequate for cytogenetic studies. The *JAK2* V617F mutation was not identified. **Table 1** summarizes the findings of all the cytogenetic studies that were done since diagnosis, along with marrow characteristics and *BCR-ABL1* KD mutations detected. **Figure 1** details the molecular response over time along with the treatment history.

The patient was immediately started on imatinib and hydroxyurea for the important leucocytosis. A BCR-ABL1 transcript level of 0.135% on the IS, was obtained in April 2009 but, in July 2009, there was a loss of the molecular response confirmed on subsequent specimens with a BCR-ABL1 transcript level of 18.2% IS in December 2009, as well as an increasing thrombocythemia. She was therefore put on dasatinib as second line treatment in February 2010. A search for mutations in the *BCR-ABL1* KD was performed at another center at the end of 2009 with two mutations identified using the amplification-refractory mutation system, specifically a G250E and an E459K. While on dasatinib, the patient only achieved

Figure 1. BCR-ABL1 transcript levels (% international scale) over time along with treatment history.

Table 1. Results of G-banding cytogenetic analyses performed on bone marrow cells in metaphase along with BCR-ABL1 transcript levels illustrating CML disease status, treatment received at the time with bone marrow characteristics and blood count results.

Date	Karyotype*	BCR-ABL1 transcript level (% International scale)†	FISH‡	Marrow characteristics	Blood count†	Treatment	BCR-ABL1 kinase domain mutation§
22/09/2008	N/A	100%	77.8%	2% blasts Very important cellularity with an important granulocytic component but no dysplasia	WBC 669.2 x 10 ⁹ /L ANC 107.2 x 10 ⁹ /L Hb 84 g/L PLT 355 x 10 ⁹ /L	Imatinib + Hydroxyurea	N/A
23/11/2009	46,XX,t(9;22)(q34;q11.2) [15] 46,XX [3] 46,XX,del(6)(q21q27),t(9;22) [3]	5.302%	0.2%	N/A	WBC 8.9 x 10 ⁹ /L ANC 5.2 x 10 ⁹ /L Hb 112 g/L PLT 1497 x 10 ⁹ /L	Dasatinib	G250E + E459K G250E + E459K + F317L
14/02/2011	N/A	14.573%	51.2%	4% blasts (no immunophenotyping) No dysplasia	WBC 6.8 x 10 ⁹ /L ANC 4.2 x 10 ⁹ /L Hb 114 g/L PLT 1218 x 10 ⁹ /L	Dasatinib → Nilotinib	F317L
05/06/2012	46,XX,-7,+22 [15] 46,XX [5]	0.0014%	0.0%	0% blasts (8% on immunophenotyping) No dysplasia	WBC 2.8 x 10 ⁹ /L ANC 1.3 x 10 ⁹ /L Hb 110 g/L PLT 253 x 10 ⁹ /L	Nilotinib	N/A
02/04/2013	N/A	Negative (no BCR-ABL1 transcript found)	N/A	0% blasts (16% on immunophenotyping) Tri-lineage dysplasia	WBC x 10 ⁹ /L ANC 0.2 x 10 ⁹ /L Hb 114 g/L PLT 158 x 10 ⁹ /L	Nilotinib	N/A
12/11/2013	46,XX,t(9;22)(q34;q11.2) [2] 46,XX,t(9;22)(q34;q11.2),t(5;20)(q32;q13) [10] 47,XX,+8 [6] 46,XX [2]	3.841%	13.7%	1% blasts (3% on immunophenotyping) Tri-lineage dysplasia	WBC 1.0 x 10 ⁹ /L ANC 0.3 x 10 ⁹ /L Hb 105 g/L PLT 177 x 10 ⁹ /L	Nilotinib + Azacitidine	N/A
13/04/2015	46,XX,t(9;22)(q34;q11.2) [5] 46,XX,t(9;22)(q34;q11.2),t(5;20)(q32;q13) [15]	3.393%	74.6%	5% blasts (7% on immunophenotyping) Tri-lineage dysplasia	WBC 11.9 x 10 ⁹ /L ANC 6.55 x 10 ⁹ /L Hb 116 g/L PLT 747 x 10 ⁹ /L	Nilotinib + Azacitidine	F317L
10/05/2016	47,XX,+8 [16] 48,XX,+8,+8 [1] 48,XX,+8,+8,+mar [1] 46,XX [3]	1.336%	2.0%	5% blasts No dysplasia	WBC 4.1 x 10 ⁹ /L ANC 2.61 x 10 ⁹ /L Hb 119 g/L PLT 76 x 10 ⁹ /L	Ponatinib	N/A
24/10/2016	47,XX,+8 [10] 46,XX [10]	0.022%	0.0%	1% blasts No dysplasia	WBC 5.9 x 10 ⁹ /L ANC 3.8 x 10 ⁹ /L Hb 133 g/L PLT 154 x 10 ⁹ /L	Ponatinib	N/A

* The number of metaphases in which the clones were identified are indicated in the brackets

† BCR-ABL1 transcript levels and blood count values obtained closest to the bone marrow biopsy are listed here since blood tests were not always obtained on the day of the biopsy. All results are within one month of the date the aspiration/biopsy was done

‡ Fluorescence in situ hybridization

§ Mutational analyses on the specimens at diagnosis, in 2009 and 2011 done using the amplification-refractory mutation system, with the analysis in 2015 done using Sanger sequencing.

a partial hematological response with persistent thrombocytosis, and the lowest BCR-ABL1 transcript level was at 2.18%. The F317L *BCR-ABL1* KD mutation was detected in another center early 2011. A mutational analysis was performed at our center at the same time but on a specimen from December 2009 and the three mutations G250E, E459K and F317L were detected. This mitigated response as well as the emergence of the F317L mutation, which is associated with dasatinib resistance [2,27], prompted a switch to nilotinib in February 2011. No family donor for a potential alloSCT was identified. A complete cytogenetic response was achieved at 4 months and a deep molecular response at 10 months without any BCR-ABL1 transcripts detected by qRT-PCR, with a detection limit of at least 1 in $10^{4.5}$ cell in our laboratory.

MDS was suspected in 2012 after the blood count revealed progressive cytopenias. Cytogenetic studies on a bone marrow specimen revealed a clonal population of Ph-negative cells in 15 metaphases harboring -7 as well as gain of chromosome 22 (+22), while the patient had a deep molecular response (defined as a BCR-ABL1 transcript level less than 0.0032%) of her CML with a BCR-ABL1 transcript level of 0.0014%. The bone marrow did not reveal any dysplasia but immunophenotyping studies did identify 8% myeloblasts. An MDS was diagnosed and azacitidine was started soon afterwards based on her high R-IPSS score. A bone marrow examination revealed tri-lineage dysplasia in April 2013, with 16% blasts on immunophenotyping. The deep molecular response to nilotinib was sustained until June 2013 when the BCR-ABL1 transcript level started to rise, with a subsequent confirmed loss of the major molecular response on a subsequent specimen in November 2013. Tri-lineage dysplasia was present in the bone marrow at this time, with cytogenetic studies revealing the presence of Ph-positive cells with t(5;20)(q32;q13) in 10 metaphases and Ph-negative cells with +8 in 6 metaphases. The clones harboring -7 and +22 were not identified. The blood count later revealed an important thrombocytosis in 2014. On control bone marrow cytogenetic studies in April 2015, the Ph chromosome was present in all metaphases, with t(5;20)(q32;q13) present in 15 metaphases. Significant tri-lineage dysplasia was present in the bone marrow. No new *BCR-ABL1* KD mutation was detected.

Nilotinib and azacitidine were stopped in January 2016 and the patient was switched to ponatinib 30 mg daily. A complete hematological response was obtained at three weeks with a major molecular response (MMR) obtained at 6 months, followed by a deep molecular response at one year. No evidence of myelodysplasia was found on two control medullary biopsies in 2016, although cells with +8 have persisted on cytogenetic studies. Ponatinib dosage was reduced to 15 mg alternating with 30 mg in January 2017 due to hypertension and sinus tachycardia, which were considered as treatment related side-effects. At two years, the molecular response is sustained with no recurrence of the MDS, and ponatinib is currently well tolerated at the adjusted doses.

Discussion

This is an interesting case because this patient, over the course of her disease, developed secondary resistance to the three TKIs approved as first-line treatment for CML, as well as developing a poor prognosis MDS according to R-IPSS. This led us to treat her with the hypomethylating agent azacitidine concurrently with nilotinib, before ultimately switching to ponatinib alone two years ago, resulting in a sustained MMR of her CML without recurrence of a MDS phenotype. Different mutations and cytogenetic abnormalities in the Ph-positive clonal population as well as CCAs in Ph-negative cells have been identified since diagnosis, with some having had important clinical consequences and therapeutic implications.

Since the introduction of imatinib, the first TKI targeting the BCR-ABL1 tyrosine kinase, four other TKIs have been approved in North America, with ponatinib being the latest and first third-generation TKI. These treatment options have revolutionized the treatment of CML with life expectancy now approaching that of the general population [28]. TKIs induce a rapid and sustained molecular response in most patients with CP-CML, with a MMR associated with a durable complete cytogenetic response [29]. However, a minority of patients, especially those presenting a high tumor burden, eventually develop resistance, with some rarely developing resistance to more than one TKI [30]. This patient harboring three *BCR-ABL1* KD mutations represents such a case as she eventually developed secondary resistance to imatinib, dasatinib and nilotinib. It is important to note that she achieved a deep molecular response to nilotinib which was subsequently lost, which is uncommon. Choice of therapy can be challenging after multiple TKI failure, with ponatinib, a newly available third-generation TKI as well as bosutinib, a second-generation TKI, remaining available options that could be tried before considering alloSCT in these patients [2,31]. AlloSCT remains a potential curative treatment for CML but is rarely performed nowadays due to the efficacy of TKIs and toxicity concerns in elderly patients [2]. Another issue specific to this case is that no reports are available that evaluate the outcome of alloSCT in cases of a MDS present concurrently with CML. Still, it was considered at the time, but no family donor was identified. An unrelated donor could have been an option, but age was initially seen as a limitation, and after discussion with the patient it was decided to try ponatinib.

Three point mutations in the *BCR-ABL1* KD were identified over the course of her disease which probably explains the acquired and sequential resistance to imatinib and dasatinib. G250E, F317L and E459K have been implicated in imatinib resistance [4,7,32]. The patient did however exhibit a significant molecular response with imatinib, suggesting that these mutations were either acquired during therapy or represented undetectable clones at diagnosis that were then selectively advantaged during TKI therapy. G250E and E459K were not detected on the last two analyses, confirming the efficacy of dasatinib in treating these clones and suggesting that they

probably were polyclonal and not compound mutations. Treatment failure to dasatinib confirms reports suggesting resistance of the F317L mutation to this TKI [2,27,33]. This mutation has been described to be sensitive to nilotinib, suggesting another mechanism of resistance was responsible for nilotinib treatment failure [32]. Ponatinib has been shown to be active against all the *BCR-ABL1* KD mutations when present individually [7].

Pathogenesis of clonal evolution of Ph-positive clones has been studied, with *BCR-ABL1* playing an important role in hindering DNA repair processes and possibly in promoting DNA damage [14-16]. This genetic instability plays a major role in the progression of CP-CML to more advanced stages of disease, with leukemic cells in BC-CML usually having accumulated many different mutations. In this patient, the first evolution of the Ph-positive cells identified was the development of *BCR-ABL1* KD mutations, with subsequent development of a Ph-positive subclonal population demonstrating t(5;20)(q32;q13). To our knowledge, this translocation has not been previously reported in CML or MDS, so its clinical significance is unclear. However, deletions and translocations involving 5q32 as well as deletions in 20q13 are associated with myeloproliferative neoplasms and MDS [23,34-36]. Most notably, 5q32 is included in the deleted region in patients with the 5q- syndrome, a sub-type of MDS [34].

Recurrent CCAs in Ph-negative cells have been described in different reports, most often involving chromosomes 7, 8 and Y, although they remain a rare occurrence, with an incidence varying between 3 and 17% [23]. The origin of such clones is subject to controversy, with different possible mechanisms proposed over the years. One hypothesis is that a pathological clonal population may precede the acquisition of the Ph chromosome, which would imply a two-step pathogenesis to CML with the first event yet-to-be-identified. However, CCAs in Ph-negative cells are most often not present in Ph-positive cells, as is the case in this report, which goes against this mechanism [18]. Initially, CCAs in Ph-negative cells were reported in patients treated with chemotherapy and interferon, suggesting that these agents might have been involved in the pathogenesis of these aberrations [17]. However, CCAs in Ph-negative cells have been described in patients treated with TKIs up-front, which prompted some to suggest that TKI toxicity could result in such aberrations [20,37,38].

Another aspect which remains controversial is the prognostic significance of these CCAs in Ph-negative cells. Only a minority of patients harbouring such an aberration will develop a second hematological malignancy such as an MDS and/or AML. As mentioned, aberrations involving chromosome 7 seem to confer the greatest risk, but the majority of such patients still don't develop a MDS/AML [19]. Transient -7 appearing during TKI therapy has also been reported [18,21,39]. In this case presentation, -7 and +22 in the same clone was the first CCA identified in Ph-negative cells and coincided with the appearance of cytopenias in June 2012. Dysplasia was not

observed on this bone marrow specimen, but it was present in April 2013 when no *BCR-ABL1* transcripts were identified using qRT-PCR, indicating that a MDS was effectively present and that the manifestations did not simply result from progression of the CML. A question raised by these observations is whether the Ph-negative clone harbouring -7 and +22 was responsible for the MDS or was simply a coincidental finding. Assuming it was responsible, another question remaining is why the myelodysplasia persisted after the disappearance of this clone. The +8 clone probably is not responsible for the MDS since it persisted after the correction of the cytopenias and the disappearance of the dysplasia in the bone marrow under ponatinib therapy. Trisomy 8 seems to represent the genetic instability of the bone marrow precursors in this patient, without necessarily representing any specific hematological disease, as has been observed in other reports [23].

The pathogenesis of MDS/AML developing during TKI therapy remains largely unclear, and it is difficult to say if they represent two manifestations of a common underlying hematopoietic disease or are two independent entities. As mentioned, only a minority of patients harboring CCAs in Ph-negative clones will develop an MDS/AML, even in patients with -7 [18,19,23]. In this report, the patient exhibited many different clonal populations over the course of her disease, suggesting the presence of an underlying susceptibility of her bone marrow progenitors to mutate, independent of their *BCR-ABL1* status. Perhaps the MDS in this case is most probably the result of the mutational burden and not just the result of a single anomaly. A search for mutations in genes other than *BCR-ABL1* has not been performed in this patient, as clinical implications of such findings remain unclear. However, a recently published case report described a patient with a CML and MDS with -7, well controlled with azacitidine and dasatinib but eventually relapsing, with de novo *KRAS*, *ASXL1* and *ETV6* gene mutations being the only new genetic anomalies identified at relapse [40]. Recent studies have also shown that such mutations are frequent in both Ph-negative and positive clone populations [41]. In MDS, some of these recurrent mutations were associated with poor survival [42]. More research is necessary to clarify the significance of these mutations in such diseases but these recent publications suggest there might be a role for molecular genetic analysis in the management of refractory CML.

Ponatinib is a multi-target TKI active against native and mutated forms of *BCR-ABL1* [5]. It has also shown in vitro activity against *FLT3*, *KIT*, *FGFR1* and *PDGFRα* [43]. When this TKI was started early 2016 in this patient, the CML had clearly relapsed with only Ph-positive clones identified on chromosome banding analyses. Significant dysplasia was still present in the marrow. If we then assume that the MDS was still present at the start of ponatinib, it remains unclear why it disappeared without any other MDS-specific treatment and if ponatinib could have had an effect on the MDS clone. On the other hand, ponatinib did not eliminate the Ph-negative

clones harbouring +8, suggesting it has little effect on this clonal population.

Conclusion

While most CP-CML patients have a sustained response to first-line TKIs, the reason why a minority of patients in CP-CML go on to develop genomic variations and a clonal evolution leading to a treatment-resistant disease, such as in this patient, remains unclear. This case raises important questions regarding the natural history of CML as well as on the clinical significance of Ph-negative clonal hematopoiesis in TKI-treated CML patients, especially in those developing a second hematologic malignancy. The origin of these Ph-negative clones and the possible role of TKIs in their pathogenesis, along with their possible relation to Ph-positive clones is an area open for research. This report illustrates the efficacy and safety of a hypomethylating agent combined with a TKI to treat an MDS as well as the CML. Finally, this report specifically emphasizes the sustained efficacy of ponatinib in treating CML refractory to multiple TKIs, as previously reported, and possibly who present multiple genomic aberrations, as is the case here. The F317L *BCR-ABL1* KD mutation was also observed to be sensitive to ponatinib, as has also been described. The possible effects of ponatinib on Ph-negative clone populations and secondary hematologic neoplasms need to be clarified.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	WM	HJO	XW	BF	DS
Research concept and design	✓	--	--	--	✓
Collection and/or assembly of data	✓	✓	✓	--	--
Data analysis and interpretation	✓	✓	✓	✓	✓
Writing the article	✓	--	--	--	--
Critical revision of the article	✓	✓	--	--	✓
Final approval of article	✓	✓	✓	✓	✓
Statistical analysis	--	--	--	--	--

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