How we will treat chronic myeloid leukemia in 2016

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Abstract

Imatinib will become generic in 2016; assuming that its price will decrease precipitously, we expect that the economic forces will change our current practice habits. We reviewed the literature on the current recommendations to treat chronic myeloid leukemia and highlight how we plan to deal with these changes. Specifically, we propose to better characterize patients according to prognostic scores, to allow more attention to those at high risk for disease progression, e.g., three-month guidelines and *BCR/ABL1* message half-time, emphasize compliance by using contemporary technologies, and increase the importance of early monitoring. We hope that our message will open communication between providers, insurance companies and healthcare authorities to offer the best care for our patients.

Keywords

Chronic myeloid leukemia; tyrosine kinase inhibitors; price of drugs; generic

Introduction

Imatinib was approved for chronic myeloid leukemia (CML) in the United States of America (USA) by the Food and Drug Administration (FDA) in 2001.[1] Since its approval, two other tyrosine kinase inhibitors (TKIs), nilotinib and dasatinib, were approved by the FDA as frontline treatment for CML based on two separate randomized trials comparing these second generation TKIs to imatinib.[2, 3] Both trials showed "faster" cytogenetic and molecular responses at 12 months with the second generation TKIs which persisted up to three years (Figures 1, Panels A and B). Dasatinib's improved cytogenetic outcome at 12 months was also confirmed by an independent trial.[4] Interestingly, high-dose imatinib

improved cytogenetic and molecular responses in one randomized study[5] but not in another.[6] Those effects were mainly observed in patients with a higher risk for disease progression based on the Sokal,[7] the Hasford[8] or the European Treatment and Outcome Study (EUTOS)[9] prognostic systems (Tables 1 and 2). Progression to accelerated/blastic phases was statistically less frequent with the use of nilotinib compared to imatinib (ENESTnd, Figure 1, Panel C). No such data are available for dasatinib or high-dose imatinib. Yet, none of these differences translated into longer disease-free or overall survival. In spite of these facts, the second generation TKIs have been adopted in the first line setting for all patients by many practitioners in the USA. Their long-term safety data are summarized in Table 3.

How will we treat this patient in 2016?

Imatinib's patent expires on February 1st, 2016. Currently, imatinib sells in the USA for $92,000 per year.[10] The second generation TKIs are even more expensive; nilotinib costs $115,500 per year and dasatinib $123,500 per year.[10] The prices for these drugs vary in other countries. For example, in the United Kingdom, imatinib and nilotinib cost the same ($33,500) while dasatinib is more expensive ($48,500). In South Africa, nilotinib is less expensive than imatinib ($28,000 vs. $43,000) and dasatinib is more expensive than imatinib ($54,500). It is logical to assume that given a broad cost differential after patent expiration, insurance companies and healthcare authorities in the USA will favor generic imatinib as of 2016. The question for clinicians in the face of this anticipated change in drug coverage is how to optimize or codify the upfront use of second generation TKIs for patients at higher risk of progression on imatinib.

Clinical Parameters for Evaluation of Treatment Response

Clinical response to TKIs is measured by three main parameters which are acknowledged by the European Leukemia Net (ELN)[11] and the National Comprehensive Cancer Network (NCCN).[12] Complete hematologic response (CHR) is defined as reduction in white blood cell count to less than 10×10^9/L, reduction in platelet count to less than 450×10^9/L, disappearance of immature cells in the peripheral blood, no signs or symptoms of disease, and disappearance of splenomegaly. Cytogenetic response is divided into complete, partial and minor responses. Complete cytogenetic response (CCyR) is defined as 0% Philadelphia-positive (Ph$^+$) metaphase cells upon evaluation of a minimum of 20 cells; partial cytogenetic response is 35% Ph$^+$ metaphase cells, and minor cytogenetic response is >35% Ph$^+$ metaphase cells. Major cytogenetic response applies only to large studies and combines complete and partial cytogenetic responses (0% to 35% metaphase cells with the Ph+ chromosome).[13]

Molecular response is the most sensitive measure currently used to monitor the disease. It is determined by quantifying the *BCR/ABL1* transcript level through quantitative real-time reverse-transcriptase polymerase chain reaction of a sample from either the peripheral blood or the bone marrow. Major molecular response (MMR), a term that arose from the International Randomized study of Interferon and STI571 (IRIS),[14] is defined as greater than 3 log reduction (<0.1%) in *BCR/ABL1* transcript level based on the International

Standard (IS).[13] The sensitivity of this assay allows for a new treatment goal of a "deep molecular response" described as 4.5-log fold reduction (MR[4.5]) of *BCR/ABL1* transcript with prognostic value for overall survival.[5] Fluctuation of *BCR/ABL1* transcript levels at the very low end of the detection level has a poor accuracy in defining a relapse risk.[15, 16] Complete molecular response denotes inability to detect the transcript.

Imatinib data indicate that timing and degree of CCyR and MMR achieved have prognostic significance. For instance, attainment of CCyR or MMR within the first 12 months of imatinib treatment predicts a low risk for disease progression (Figure 2).[13, 17] Furthermore, achievement of MMR in the first year indicates long-lasting CCyR.[13] However, waiting for 12 months is not appropriate and therefore several groups have looked at earlier time points. The three-month time point was chosen by the ELN[11] and the NCCN[12] as a decision point based on imatinib data showing better outcome if patients achieved 10% or less *BCR/ABL1* transcript by IS at the three-month time point (Figure 3, Panel A).[18, 19] Others have challenged this time point and proposed the six-month time point, especially when using second generation TKIs because of their more robust response.[20] When one compares nilotinib to imatinib data from ENESTnd, (Figure 3, Panel B) one can clearly notice that 33% of patients on imatinib did not achieve the 10% *BCR/ABL1* message level by IS at the three-month time point and those patients are at risk for disease progression,[21] especially if they had intermediate or high Sokal or Hasford Scores at diagnosis.[3] However, no data showing that a change in treatment will modify the prognosis of these patients are available. A study offering nilotinib (400 mg orally twice daily) for patients with suboptimal response by ELN[11] showed improved responses in some patients but many did not achieve CCyR.[22] It is possible that patients with suboptimal responses inherently have worse disease and therefore are likely to progress regardless of change in treatment.[19] We propose the three-month time point as a decision point because we predict that generic imatinib will become the drug of choice based on insurance coverage after 2016, and we therefore should be monitoring these patients more closely for disease progression. Alternatively, though with minimal data on longer disease-free or overall survival, insurance companies and healthcare authorities should be encouraged to pay for the use of second generation TKIs for all patients with intermediate and high Sokal, Hasford or EUTOS scores at the time of diagnosis given their higher risk of disease progression and imatinib failure.

Two randomized studies, ENESTnd and dasatinib vs. imatinib (DASISION), have taught us that patients at low risk by either Sokal or Hasford prognostic systems are less likely to progress to accelerated/blastic phase when treated with either imatinib or the second generation TKIs. However, patients at the intermediate- and high-risk groups (Table 2) are less likely to benefit from imatinib.[23, 24] These prognostic systems (Table 1) should therefore be calculated on all newly diagnosed CML patients.[7–9] Such applications currently exist for free on the web (e.g., http://bloodref.com/myeloid/cml/sokal-hasford).

Adherence and Compliance to Therapy

Adherence to treatment is a challenge for many of the patients who are on chronic therapy for any medical condition. The ADAGIO study[25] was the first to demonstrate that only 14.2% of CML patients were perfectly adherent with 100% of prescribed imatinib. That

study covered only 90 days. A study covering a two-year period in patients with CML or gastrointestinal stromal tumors showed 78% adherence to imatinib.[26] Furthermore, this study showed that adherence decreased with imatinib doses above 400 mg daily.[26] In the United Kingdom, a study was carried out on 87 patients diagnosed with chronic phase CML and treated with imatinib 400 mg/day for a median of 59.7 months.[27] This study reported a median imatinib adherence rate of 98%, however about 26% of the patients had <90% adherence and 14% had <80% adherence.[27] Several studies have shown similar rates of non-adherence in patients treated with nilotinib and dasatinib. Santoleri *et al*[28] have shown that adherence to nilotinib was at 0.93 compared to 0.83 with imatinib and 0.85 with dasatinib; however decreased adherence was seen in all three drug treatment cohorts over time. Important factors contributing to non-adherence include drug interactions, adverse reactions, and mental burden of the disease along with forgetfulness of daily dosing. Non-adherence to treatment leads to reduced drug levels resulting in reduced efficacy and potential for loss of response.

Telemonitoring or remote monitoring is a valuable tool currently in development by several pharmaceutical companies. There are two concepts behind the technology. The first is a medication with an implanted ingestible sensor. The medication is ingested by the patient and becomes activated in the stomach and the data are transmitted to a receiver patch on the patient's abdomen. That data can be visualized on a Smartphone or a computer. In case of missed dosages, the patient can be contacted directly by the provider's office for reminders.

The second strategy measures adherence based on the patient opening his/her pill bottle, e.g., GlowCap© by Vitality™ (available through different vendors) or MEMS® medication bottle with TrackCap™. These are pill bottles which have an embedded sensor in the bottle cap that sends a signal to a nightlight sensor which has a reminder light and plays a ring tone. The sensor senses and sends a signal to the nightlight receiver each time the bottle has been opened signifying patients administering their pills and thus indicating compliance. The reminder light flashes for an hour from the time of dosing. If the bottle is not opened within this window, the receiver will play a ring tone every few minutes until the bottle has been opened. If the bottle is not opened, a phone call from a monitoring unit will advise the patient or his/her designee about the "missed dosage." Clearly, patients can open the bottle and not take the medication. A small study performed in February of 2009 by Vitality™, where GlowCaps were used as an intervention and adherence was measured over 3 months, showed improved average adherence rate of 86% compared to 50%. Another trial is currently in progress (NCT01490983). GlowCapc also has a "press to refill" capability which is targeted to improve patient compliance by sending a request for a medication refill to the patient's pharmacy with just the press of a button on the pill bottle.

With increasing technological progress to simplify complex treatment regimens, medication adherence is likely to improve; however it cannot completely replace the encouragement patients receive from physical interaction. The ADAGIO study[25] clearly showed that the duration of the visits, number of patients followed by that center, etc., which characterize the physician/patient relationship, are the most important factors modifying medication adherence. In addition, a team approach, consisting of a social worker, nurse and pharmacist assisting the provider, has the potential to increase adherence.[29] For patients with CML

where adherence translates into the difference between long term cancer control and refractory disease or progression to a blastic phase, efforts to increase adherence through novel ideas is as important as the physician/patient relationship.

Intolerance

The question remains what treatment to choose if patients develop intolerance to TKIs that significantly affects their quality of life. We propose to switch the patient to another TKI without hesitation because we are concerned that patients who develop such intolerance will not be compliant with their medication and the immediate corollary will be the development of resistance.

Resistance

Resistance is divided into primary and secondary based on the timing. Primary resistance occurs when goal responses are never achieved with frontline therapy. Secondary resistance develops after a targeted response to a frontline therapy was achieved but subsequently lost. Outcome in the latter case is better. At 60-month follow up from IRIS, 6% progressed to accelerated/blastic phases, 3% had hematologic relapse, 5% lost their cytogenetic response and 2% died of causes unrelated to CML.[14] In the three-year follow-up of ENESTnd, 0.7% of patients progressed on nilotinib compared with 3.5% on imatinib.[23] In the three-year follow-up of DASISION, 7% of patients progressed on each arm.[24] The main mechanism of both primary and secondary resistance to TKIs is the development of mutations, occurring in about 50% of the patients followed by other mechanisms such as overexpression of *BCR/ABL1*, increased expression of adhesion molecules such as *CXCR4*, increased expression of multi-drug resistance proteins, and unique to imatinib, decreased expression of influx proteins such as organic cation transporter 1.[20]

There are currently four TKIs available for imatinib failures. Choice of another TKI following development of resistance to imatinib is largely based on side effect profile. For example, a patient with history of pancreatitis or with increased risk for arterial thrombosis (e.g., diabetic patient with intermittent claudication) will not be an optimal candidate for nilotinib. Other side effects associated with nilotinib, are myelosuppression, QT prolongation, and hyperglycemia. Similarly, most physicians would be reluctant to initiate dasatinib in a patient with a history of pulmonary hypertension. Other side effects associated with dasatinib include myelosuppression, bleeding related events, fluid retention, QT prolongation and congestive heart disease. While nilotinib and dasatinib have been used by the community for a long time, bosutinib and ponatinib were approved in 2013. Bosutinib is associated with temporary and self-limiting diarrhea, myelosuppression, hepatic toxicity, and fluid retention, but of note, has not been reported to be associated with only minimal cardiac side effects.[30]

Ponatinib is unique in that it is the only BCR/ABL1 inhibitor with demonstrated efficacy against all *ABL1* mutations,[31] although resistance with compound mutations may arise.[32] Ponatinib was recently linked to an increased rate of thromboembolic phenomena.[33] We expect that the mechanism(s) of these phenomena and ways to mitigate them will be described within the next year and those will lead to potential broader use of this drug. Other

side effects associated with ponatinib include heart failure, hepatotoxicity, hypertension, pancreatitis, neuropathy, ocular toxicity, bleeding events, fluid retention, arrhythmias and myelosuppression. At this point, given the significant side effect profile, treatment with ponatinib is restricted to patients with the T315I mutation and for those for whom no other TKI is indicated.

The question will remain what to offer a patient who has failed imatinib as well as a second TKI therapy. The dilemma would be whether to offer the patient treatment with ponatinib, abandon all TKIs and switch to a non-TKI approach with omacetaxine, or proceed onto an allogeneic stem cell transplantation (allo-SCT).

Omacetaxine mepesuccinate, a plant alkaloid and protein synthesis inhibitor, is a novel molecule which has shown activity against cells with T315I mutation harboring cells *in vitro*.[34, 35] A phase II trial involving a total of 62 patients showed CHR achievement in 77% of patients with median response duration of 9.1 months.[35] Furthermore, the trial demonstrated a median progression free-survival of 7.7 months. Twenty three percent of patients achieved a major cytogenetic response, and 16% complete cytogenetic response.[35] Non-hematologic adverse reactions included infection, diarrhea, and nausea which were Grade 1/2.[35] Thus, omacetaxine is a non-TKI therapeutic agent with significant activity in CML.

Allo-SCT remains the only curative treatment in CML. Its mechanism of action is immunologically mediated and can induce eradication of the leukemic stem cells. In the pre-TKI era, allo-SCT was the frontline treatment of choice for young patients with CML with good performance status.[36] However since the establishment of imatinib as frontline therapy, the three main indications for allo-SCT in patients with CML remain those in blastic phase, patients with multiple TKI failures or (rarely) intolerance, and patients with TKI-resistance mutations.[37] A study by Jabbour *et al* demonstrated that allo-SCT was an important salvage treatment alternative for patients with TKI-resistant CML.[38] Ten patients with imatinib resistance (nine with CML, one with acute lymphoblastic leukemia) underwent engraftment following allo-SCT.[38] Three patients died of relapse post-allo-SCT whereas seven patients were alive for at least 19 months.[38] For the imatinib-resistant mutants and even the challenging T315I mutants, allo-SCT remains a viable treatment option and it should be considered.

Faster and deeper response and treatment discontinuation

The imatinib discontinuation trials demonstrated approximately 50% rate of disease relapse.[39–41] The hypothesis is that faster and deeper response would result in significantly less disease relapse after second generation TKI discontinuation. This is currently being tested in several clinical trials (NCT01698905, NCT01744665, NCT01627132, NCT01850004, NCT01804985 and NCT01887561). If this hypothesis is substantiated, there will be significant clinical, financial and quality of life merit to the use of second generation TKIs upfront for newly diagnosed patients.

Conclusions

With medical progress, CML has been made into a truly chronic disease. With the recent approval of newer and more efficacious TKIs and the expected availability of generic imatinib in 2016, treatment decisions for newly diagnosed chronic phase CML will become increasingly complex. We propose here that all newly diagnosed chronic phase CML patients be stratified based on their risk scores to receive either upfront imatinib versus second generation TKI therapy. While patients with low Sokal/Hasford/EUTOS appear to benefit from imatinib, close attention will have to be paid to those in the intermediate/high risk scores for whom the risk of development of primary resistance is higher. In addition, close attention will have to be paid to compliance, using currently available technology to reduce the risk of developing resistance. Finally, decisions about second and third line approaches will need to be weighed against possible resistant mechanism(s) with due consideration of the use of ponatinib, non-TKI based therapy with omacetaxine and/or allo-SCT, in the appropriate clinical scenarios.

Acknowledgments

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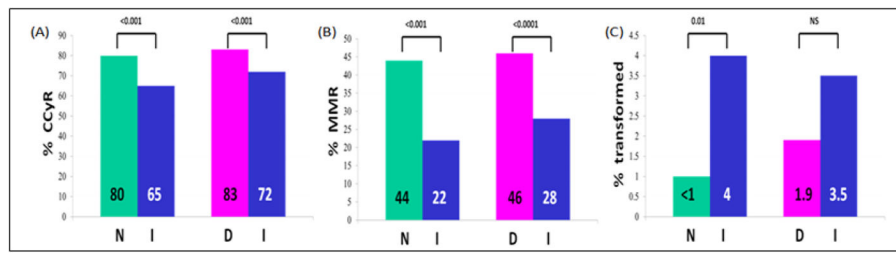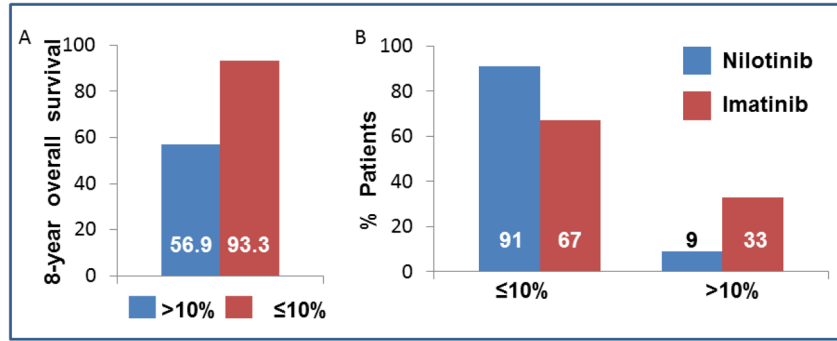
Figure 1.

Response to nilotinib and dasatinib compared to imatinib. Panel A and B demonstrate complete cytogenetic response (CCyR) and major molecular response (MMR) achieved at 12 months in ENESTnd [nilotinib (N) vs. imatinib (I)] and DASISION [dasatinib (D) vs. imatinib (I)] trials. Panel C shows progression to accelerated/blastic phase with nilotinib (N) and dasatinib (D) in comparison to imatinib (I), at the conclusion of the first 12 months of follow-up. Numbers at the top represent P values.
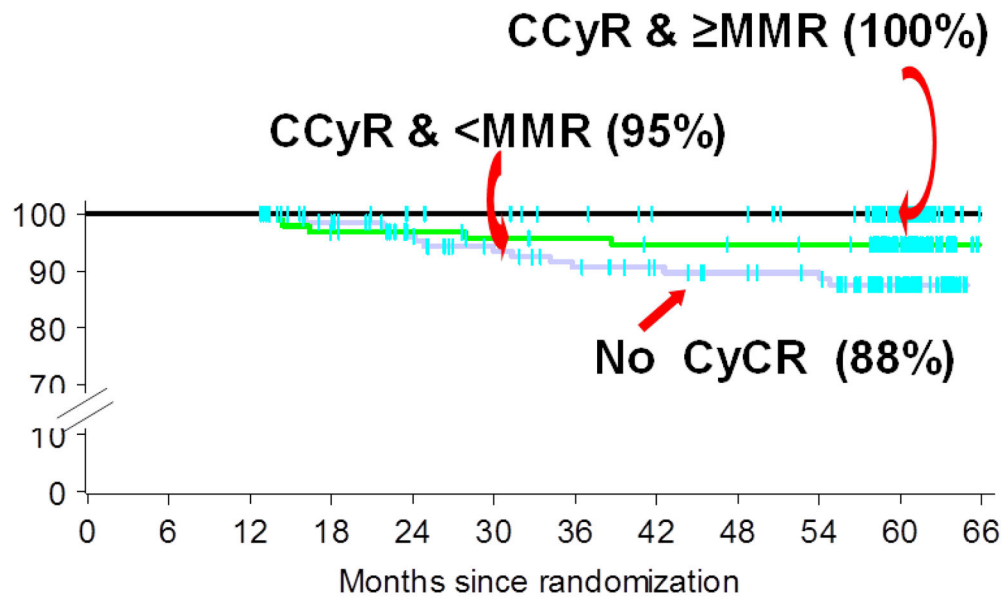
Figure 2.
Survival of newly diagnosed CML patients. Data from IRIS showed that for patients who did not achieve CCyR within the first 12 months of imatinib treatment fared worse. Adapted from Druker et al., New Engl J Med 355:2408–17, 2006 with Permission. Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response.

Figure 3.
The effect of *BCR/ABL1* message measured by International Standard scale at 3 months. Panel A, Overall 8 year survival for patients who achieved molecular response at 3 months from the IRIS. Patients with *BCR/ABL1* transcript levels of >10% (n = 68) at 3 months had significantly lower 8-year overall survival (56.9%, p<0.001) compared to patients with transcript levels <10% who had overall survival of 93.3% over 8 years (p<0.001). Panel B demonstrates achievement of *BCR/ABL1* message level at three-month time point from ENESTnd.

Table 1

Current prognostication systems for chronic myeloid leukemia.

Parameters	Sokal Risk Score	Hasford Risk Score	EUTOS score
Age (years)	*0.116 (Age − 43.4)*	0.666 when Age 50	
Spleen (cm)	0.0345 (Spleen − 7.51)	0.042 x Spleen	0.0402 x Spleen
Platelet Count (x10⁹/L)	0.188 [(Plt/700)²−0.563]	1.0956 when Platlet 1500	
Blood Myeloblasts (%)	0.0887 (Myeloblasts -2.10)	0.0584 x Myeloblasts	
Blood Basophils (%)	-	0.20399 when Basophils >3%	0.07 x Basophils
Blood Eosinophils (%)	-	0.0413 x Eosinophils	
Relative Risk	Exponential of the Total	Total x1000	
Low Risk	<0.8	780	87
Intermediate Risk	0.8 – 1.2	781–1480	
High Risk	>1.2	>1480	<87

Abbreviations: EUTOS, EUropean Treatment and Outcome Study.

Table 2

Patients stratified by Sokal risk score and response to imatinib and nilotinib.

Sokal Risk *Imatinib (IRIS)*	Low Risk (%)		Intermediate Risk (%)		High Risk (%)	
CCyR (p<0.001)	89		82		69	
Disease progression at 60 months	3		8		17	
No disease progression in patients with CCyR	99		95		95	
Nilotinib vs. imatinib (ENESTnd)	**I**	**N**	**I**	**N**	**I**	**N**
Best cumulative MMR by 3 years*	62.5	76.7	54.5	75.2	38.5	66.7

*
After the 2-year visit, cytogenetic assessments were not required for all patients, hence no CCyR rates are available.

Abbreviations: CCyR, complete cytogeneric remission; I, imatinib; IRIS, International Randomized study of Interferon and STI571; N, nilotinib.

Table 3

Long-term safety data for Imatinib, nilotinib and Dasatinib. Data are presented as percentages (unless otherwise described); data were extracted from IRIS, ENESTnd and DASISION trials.

	Imatinib	Nilotinib[*]	Dasatinib
Anemia	5.7	3.9–4.7	6–11
Neutropenia	21.4	10.8–11.8	15–24
Thrombocytopenia	8.9	10.4–12.3	10–19
Nausea/Vomiting	20–10	11–19/5–9	10/5
Diarrhea	21	6–8	21
Fluid Retention	56.4	18.6–23.5	13
Effusions	1.8	0.7–1.8	19
Myalgia	12	--	23
Muscle Inflammation	17	--	4
Musculoskeletal pain	14	--	11
Muscle Spasm	24	6–7	--
Fatigue	10	--	9
Rash	22.1	41.2–46.9	13
Alopecia	4	8–13	--
Pruritus	5	13–15	--
Headache	10	14–21	13
Pulmonary Arterial Hypertension	0	--	8 patients
Peripheral Arterial Occlussive Disease	0	1.1–1.4	--
Ischemic Heart Disease	1.1	3.2–4	--
An increase of >60 miliseconds in QTcF from baseline	0.4	0.4–1.1	--
Hypophosphatemia	28	5	7
Pancreatitis	0.7	1.8–2.2	--
Hepatotoxicity	2.5	1.4–4	--
Glucose increased	0	5.4–6.1	--

[*] Data include toxicities from both nilotinib 300 mg twice daily and 400 mg twice daily.