Published in final edited form as:

Cancer Chemother Pharmacol. 2012 August ; 70(2): 345–350. doi:10.1007/s00280-012-1881-3.

Concurrent use of proton pump inhibitors or H2 blockers did not adversely affect nilotinib efficacy in patients with chronic myeloid leukemia

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Abstract

Purpose—The impact of proton pump inhibitors (PPIs) and histamine H2 receptor antagonists (H2 blockers) on the efficacy of nilotinib was evaluated.

Methods—Retrospective analyses were performed in patients with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP; $N = 492$) and in patients with imatinib-resistant or -intolerant Ph+ CML-CP ($N = 256$) treated with nilotinib.

Results—In the newly diagnosed population, 87 (17.7%) and 49 (10.0%) patients received PPIs and H2 blockers, respectively. Major molecular response at 12 months was achieved by 59 (49.6%) patients who received at least one PPI or H2 blocker ($n = 119$) and 153 (41.0%) patients who did not receive any comedication ($n = 373$; $P = 0.13$). PPIs and H2 blockers were used by 77 (30.1%) and 17 (6.6%) patients with imatinib-resistant or -intolerant CML-CP, respectively. Major cytogenetic response by 12 months was achieved by 55 (64.0%) patients who received at least one PPI or H2 blocker ($n = 86$) versus 98 (57.6%) patients who did not receive any comedication ($n = 170$; $P = 0.40$); 39 (45.3%) versus 65 (38.2%), respectively, achieved complete cytogenetic response by 12 months ($P = 0.34$). Similar findings were observed in patients who received comedication for >50% of the time on nilotinib therapy. Nilotinib steady-state trough concentration was not affected by the presence of PPIs or H2 blockers.

Conclusions—Concurrent use of PPIs or H2 blockers did not affect the pharmacokinetics and efficacy of nilotinib in patients with Ph+ CML-CP.

Keywords

Nilotinib; drug-drug interactions; proton pump inhibitors; H2 blockers; chronic myeloid leukemia

Introduction

Nilotinib (Tasigna[®], Novartis Pharmaceuticals Corporation), a potent and selective BCR-ABL tyrosine kinase inhibitor (TKI), is approved worldwide at a dose of 400 mg twice daily for patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP) and accelerated phase who are resistant to or intolerant of imatinib. The drug was also recently approved for the treatment of patients with newly diagnosed Ph+ CML-CP at a recommended dose of 300 mg twice daily.

In the phase II registration trial of nilotinib in patients with Ph+ CML-CP resistant or intolerant to prior imatinib therapy, overall rates of major cytogenetic response (MCyR) and complete cytogenetic response (CCyR) were 59% and 44% with 24 months follow-up [1]. The overall survival rate at 24 months was 87%. Nilotinib was generally well tolerated; nonhematologic adverse events were mainly grade 1/2. In patients with newly diagnosed Ph+ CML-CP, nilotinib continues to demonstrate superior efficacy with significantly improved disease control versus imatinib with 24 months follow-up in the randomized, phase III Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) trial [2]. By 24 months, major molecular response (MMR) was reported in 71%, 67%, and 44% of patients in the nilotinib 300-mg twice-daily, 400-mg twice-daily, and imatinib arms, respectively ($P < 0.0001$ for both nilotinib arms vs imatinib). Significantly fewer patients progressed to accelerated phase/blast crisis in both nilotinib arms versus the imatinib arm.

Nilotinib is administered orally and has pH-dependent aqueous solubility, with lower dissolution at higher pH. Thus, there exists a potential for interaction between nilotinib and gastric pH-elevating agents. Concurrent administration of the potent proton pump inhibitor (PPI) esomeprazole was found to cause a dramatic increase in gastric pH but only a 27% reduction in overall nilotinib exposure (area under the plasma concentration time curve [AUC]) in a study of healthy volunteers [3]. It is uncertain whether such a modest reduction in nilotinib exposure would have any clinically meaningful impact on nilotinib therapy. In addition, patients may take different types of gastric pH-elevating agents, either concurrently with the administration of nilotinib or with separate or staggered dosing. These different modes of use could also have differential impact on the clinical outcome of nilotinib treatment. In this report, we evaluated the impact of gastric pH-elevating agents, such as PPIs and histamine 2 receptor antagonists (H2 blockers), on the efficacy of nilotinib in patients with CML.

Materials and methods

Study design

Retrospective analyses were conducted in patients with imatinib-resistant or -intolerant Ph+ CML-CP registered to study CAMN107A2101 [1, 4] and in those with newly diagnosed Ph+ CML-CP registered to ENESTnd (study CAMN107A2303) [2, 5]. Both studies were conducted in accordance with the Declaration of Helsinki, and the protocols were reviewed by the ethics committee or institutional review board at each participating institution. All patients gave written informed consent.

The design and methodology of both studies have been reported previously [1, 2, 4, 5]. In the phase II registration study (CAMN107A2101), the efficacy and safety of nilotinib 400 mg twice daily was evaluated in 321 patients with imatinib-resistant or -intolerant Ph+ CML-CP [4]. ENESTnd was a phase III, open-label, multicenter study in which 846 adult patients with newly diagnosed Ph+ CML-CP were randomly assigned to nilotinib 300 mg twice daily ($n = 282$) or 400 mg twice daily ($n = 281$) or imatinib 400 mg once daily ($n = 283$) [5]. In both study protocols, concurrent use of PPIs or H2 blockers was permitted. However, concomitant administration of medications known to be strong CYP3A4 inhibitors or inducers or to have the potential to prolong the QTc interval was not allowed. Patients were also instructed to avoid grapefruits, star fruits, pomegranates, and Seville oranges or juices and products containing these fruits.

Analysis of concurrent use of PPIs or H2 blockers

The frequency and duration of concurrent use of PPIs or H2 blockers during nilotinib treatment was assessed in both studies. For ENESTnd, the relationship of these parameters to MMR at 12 months (primary efficacy endpoint) was assessed, and for study CAMN107A2101, their relationship to MCyR by 12 months (primary efficacy endpoint) and CCyR by 12 months (secondary efficacy endpoint) was assessed. Comparison of response rates in patients who received at least one PPI or H2 blocker for any duration during nilotinib therapy versus those who did not receive any of these agents was made by chi-square tests.

The H2 blockers cimetidine and ranitidine are also reported to be weak inhibitors of CYP3A4 [6, 7]. Thus, in addition to decreasing nilotinib concentrations through elevation of gastric pH, they may also increase nilotinib concentrations by inhibiting the CYP3A4-mediated liver metabolism of nilotinib. To avoid this potential confounding effect, a subanalysis was performed excluding cimetidine and ranitidine from the H2-blockers group.

Because the duration of concurrent use of PPIs or H2 blockers varied and was brief in some patients, a second subanalysis was performed in patients who received PPIs or H2 blockers for >50% of the time while on nilotinib therapy (i.e., longer than 6 months). Comparison of response rates in such patients versus those who had responses but received PPI or H2 blockers for $\leq 50\%$ of the time was made by chi-square tests.

Population pharmacokinetic analysis

The effect of concurrent use of PPIs or H2 blockers on nilotinib concentrations was also assessed in a population pharmacokinetic (PK) analysis of a subgroup of patients in ENESTnd who received nilotinib 300 mg twice daily or 400 mg twice daily and had nilotinib PK data available. Nilotinib trough ($C_{\min}$) PK samples were collected prior to the morning dose on day 8 of month 1 and at the end of months 3, 6, 9, and 12 after the initiation of nilotinib therapy. Thus, each patient contributed up to five $C_{\min}$ PK samples. These samples were categorized into the following four groups according to whether the patient received comedications when the PK sample was collected: PPI (patient received at least one PPI); H2 blocker (patient received at least one H2 blocker); PPI or H2 blocker (patient received at least one PPI or H2 blocker); None (patient did not receive a PPI or H2 blocker). Concentration was considered as steady state if the PK sample was taken within ± 3 hours of the scheduled time (i.e., between 9 and 15 hours after the previous dose) and after at least 3 days of nilotinib dosing without any dose interruption or modification.

Serum concentrations of nilotinib were measured using a validated liquid chromatography–tandem mass spectrometry assay at the Novartis Institutes for Biomedical Research, East Hanover, New Jersey, as previously described [8]. Using 100 μ L of serum sample, the lower limit of quantification was determined to be 2.5 ng/mL. For CAMN107A2101, within-study assay validation showed a precision of 3.7–9.2% for quality control samples at concentrations of 2.5 ng/mL to 5,000 ng/mL, and the accuracy ranged from 98.2%–101.7%. In ENESTnd, within-study assay precision was 2.1–5.6%, and the accuracy ranged from 98.8–101.0%.

Results

Concurrently used PPIs included esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. H2 blockers included cimetidine, famotidine, and ranitidine.

In total, 119 (24.2%) of 492 newly diagnosed patients from ENESTnd received PPIs or H2 blockers for any duration (median duration: 137 and 33 days for PPIs and H2 blockers, respectively) while on nilotinib therapy; 46 (9.3%) patients received this concurrent medication for >50% of the time (Table 1). Major molecular response at 12 months was achieved by 59 of 119 (49.6%) patients who received at least one PPI or H2 blocker compared with 153 of 373 (41.0%) patients who did not receive any of these agents ($P = 0.13$, chi-square test; Table 2). A similar trend, in which the MMR rate was slightly numerically higher in the group of patients who received at least one PPI or H2 blocker, was observed in each of the individual nilotinib arms.

Overall, 86 of 256 (33.6%) patients with imatinib-resistant or -intolerant Ph+ CML-CP from study CAMN107A2101 received PPIs or H2 blockers for any duration (median duration: 177 and 96 days for PPIs and H2 blockers, respectively) while on nilotinib therapy; 59 of 256 (23.0%) patients received the concurrent medication >50% of the time (Table 1).

Major cytogenetic response by 12 months was achieved by 55 of 86 (64.0%) patients who received at least one PPI or H2 blocker compared with 98 of 170 (57.6%) patients who did

not receive any of these comedications ($P = 0.40$, chi-square test). Complete cytogenetic response by 12 months was achieved in 39 of 86 (45.3%) compared with 65 of 170 (38.2%) patients, respectively ($P = 0.34$, chi-square test; Table 2). When excluding cimetidine and ranitidine from the H2-blocker group, response rates remained slightly numerically higher in the group of patients from both studies who received at least one PPI or H2 blocker.

In the subgroup of patients who received PPIs or H2 blockers for >50% of the time on nilotinib therapy, the response rates also appeared to be slightly numerically higher than those in patients who did not receive any of these comedications. No statistically significant differences were noted for patients who had responses and received PPIs or H2 blockers for >50% of the time versus those who had responses but received PPIs or H2 blockers for 50% of the time (Table 2).

Median steady-state nilotinib C_{min} was found to be similar in the presence or absence of PPIs or H2 blockers (Figs. A and B). This trend was not affected by the exclusion of cimetidine and ranitidine from the H2-blockers group (Figs. C and D).

Discussion

Reduced oral absorption and lower systemic exposure because of decreased gastric acidity in the presence of PPIs or H2 blockers has been reported for a number of drugs, including the TKIs dasatinib [9, 10] and erlotinib [11] and the HIV-1 protease inhibitors atazanavir [12] and indinavir [13]. The extent of such drug-drug interactions was found to vary among TKIs. While the overall AUC of dasatinib was reduced by 60–80% when coadministered with H2 blockers or PPIs [9, 10] and erlotinib AUC was reduced by 46% when coadministered with omeprazole [11], concomitant administration of omeprazole did not alter the PK of imatinib [14]. In this report, we evaluated the impact of PPIs and H2 blockers on the efficacy of nilotinib in patients with CML enrolled in two major clinical trials. The results suggest that the concurrent use of PPIs or H2 blockers, with the pattern identified in the two clinical trials, did not affect the PK and efficacy of nilotinib in newly diagnosed or imatinib-resistant/-intolerant Ph+ CML-CP patients treated with nilotinib.

In a previous study in healthy volunteers, a 27% reduction in nilotinib AUC was observed in the presence of esomeprazole [3]. However, in the current population PK analysis, concurrent use of PPIs or H2 blockers was not found to significantly affect nilotinib C_{min} . This is not surprising because the healthy volunteer study was conducted with a high dose of esomeprazole (40 mg once daily) to evaluate the maximum drug–drug interaction effect likely to be observed in the clinic. Esomeprazole at this dose has been shown to maintain an intragastric pH >4 for a significantly longer duration (13.2–26.1% longer over a 24-hour period) and to induce a higher median intragastric pH over 24 hours compared with standard doses of H2 blockers and omeprazole, lansoprazole, pantoprazole, and rabeprazole (mean 24-hour median gastric pH was 4.3–4.9 for esomeprazole 40 mg once daily, 3.6 for 20 mg omeprazole once daily, 3.8 for lansoprazole 30 mg once daily, 3.7 for pantoprazole 40 mg once daily, and 3.5 for rabeprazole 20 mg once daily) [15, 16]. Additionally, nilotinib was administered in the healthy volunteers study at the time when gastric pH was expected to be maximally elevated by esomeprazole [3]. Thus, the observed 27% decrease in nilotinib AUC

associated with concurrent esomeprazole in the healthy volunteer study probably represented the maximal interaction effect for nilotinib with PPIs or other gastric pH-elevating agents.

On the basis of the rates of MCyR, CCyR, and MMR, the efficacy of nilotinib did not appear to be affected by concurrent administration of PPIs or H2 blockers. In fact, response rates in both newly diagnosed patients (MMR at 12 months) and imatinib resistant- or intolerant-patients (MCyR and CCyR by 12 months) were slightly higher in patients who received at least one PPI or H2 blocker. This may be a random result of the small sample size or could be the result of unidentified mechanisms. In vitro, pantoprazole and esomeprazole could exert an inhibitory effect on ABCB1 [17] or ABCG2 [18] transporters and significantly increase the intracellular uptake and retention of nilotinib into leukemic cells in a concentration-dependent manner [19]. These observations seem to provide a possible explanation for the results of our analysis, although the high concentrations of pantoprazole and esomeprazole used in the in vitro study may not be directly clinically relevant.

Limitations of our analysis included that it was retrospective, based on 12 months of clinical data in which concurrent use of PPIs or H2 blockers was brief in some patients. In addition, the sample size was relatively small, specifically the group of patients who received PPIs or H2 blockers. Therefore, further evaluation of the long-term efficacy of nilotinib with concurrent use of PPI or H2 blockers in a larger patient population is warranted to confirm these findings.

References

1. Kantarjian HM, Giles FJ, Bhalla KN, Pinilla-Ibarz JA, Larson RA, Gattermann N, Ottmann OG, Hochhaus A, Radich JP, Saglio G, Hughes TP, Martinelli G, Kim DW, Shou Y, Gallagher NJ, Blakesley R, Baccarani M, Cortes J, le Coutre PD. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase following imatinib resistance or intolerance: 24-month follow-up results. *Blood*. 2011; 117:1141–1145. [PubMed: 21098399]
2. Kantarjian HM, Hochhaus A, Saglio G, De Souza C, Flinn IW, Stenke L, Goh Y, Rosti G, Nakamae H, Gallagher NJ, Hoenekopp A, Blakesley RE, Larson RA, Hughes TP. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. *Lancet Oncol*. 2011; 12:841–851. [PubMed: 21856226]
3. Yin OQP, Gallagher N, Fischer D, Demirhan E, Zhou W, Golor G, Schran H. Effect of the proton pump inhibitor esomeprazole on the oral absorption and pharmacokinetics of nilotinib. *J Clin Pharmacol*. 2010; 50:960–967. [PubMed: 20498287]
4. Kantarjian HM, Giles F, Gattermann N, Bhalla K, Alimena G, Palandri F, Ossenkoppele GJ, Nicolini FE, O'Brien SG, Litzow M, Bhatia R, Cervantes F, Haque A, Shou Y, Resta DJ, Weitzman A, Hochhaus A, le Coutre P. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood*. 2007; 110:3540–3546. [PubMed: 17715389]
5. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA, Kantarjian HM. the ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010; 362:2251–2259. [PubMed: 20525993]
6. Martinez C, Albet C, Agundez JA, Herrero E, Carrillo JA, Marquez M, Benitez J, Ortiz JA. Comparative in vitro and in vivo inhibition of cytochrome P450 CYP1A2, CYP2D6, and CYP3A by H2-receptor antagonists. *Clin Pharmacol Ther*. 1999; 65:369–376. [PubMed: 10223772]

7. Rendic S, Ruf HH, Weber P, Kajfez F. Cimetidine and ranitidine: their interaction with human and pig liver microsomes and with purified cytochrome P-450. *Eur J Drug Metab Pharmacokinet.* 1984; 9:195–200. [PubMed: 6097454]
8. Yin OQ, Gallagher N, Li A, Zhou W, Harrell R, Schran H. Effect of grapefruit juice on the pharmacokinetics of nilotinib in healthy participants. *J Clin Pharmacol.* 2010; 50:188–194. [PubMed: 19948946]
9. Eley T, Luo FR, Agrawal S, Sanil A, Manning J, Li T, Blackwood-Chirchir A, Bertz R. Phase I study of the effect of gastric acid pH modulators on the bioavailability of oral dasatinib in healthy subjects. *J Clin Pharmacol.* 2009; 49:700–709. [PubMed: 19395585]
10. Takahashi N, Miura M, Niioka T, Sawada K. Influence of H₂-receptor antagonists and proton pump inhibitors on dasatinib pharmacokinetics in Japanese leukemia patients. *Cancer Chemother Pharmacol.* 2011 Dec 7. 2011. Epub ahead of print.
11. OSI Pharmaceuticals, LLC. Tarceva[®] (erlotinib) Prescribing information. Farmingdale, NY, USA: 2010.
12. Tomilo DL, Smith PF, Ogundele AB, Difrancesco R, Berenson CS, Eberhardt E, Bednarczyk E, Morse GD. Inhibition of atazanavir oral absorption by lansoprazole gastric acid suppression in healthy volunteers. *Pharmacotherapy.* 2006; 26:341–346. [PubMed: 16503713]
13. Burger DM, Hugen PW, Kroon FP, Groeneveld P, Brinkman K, Foudraïne NA, Sprenger H, Koopmans PP, Hekster YA. Pharmacokinetic interaction between the proton pump inhibitor omeprazole and the HIV protease inhibitor indinavir. *AIDS.* 1998; 12:2080–2082. [PubMed: 9814882]
14. Egorin MJ, Shah DD, Christner SM, Yerk MA, Komazec KA, Appleman LR, Redner RL, Miller BM, Beumer JH. Effect of a proton pump inhibitor on the pharmacokinetics of imatinib. *Br J Clin Pharmacol.* 2009; 68:370–374. [PubMed: 19740393]
15. Miner P Jr, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am J Gastroenterol.* 2003; 98:2616–2620. [PubMed: 14687806]
16. Rohss K, Lind T, Wilder-Smith C. Esomeprazole 40 mg provides more effective intragastric acid control than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with gastro-oesophageal reflux symptoms. *Eur J Clin Pharmacol.* 2004; 60:531–539. [PubMed: 15349707]
17. Pauli-Magnus C, Rekersbrink S, Klotz U, Fromm MF. Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein. *Naunyn Schmiedeberg's Arch Pharmacol.* 2001; 364:551–557. [PubMed: 11770010]
18. Suzuki K, Doki K, Homma M, Tamaki H, Hori S, Ohtani H, Sawada Y, Kohda Y. Co-administration of proton pump inhibitors delays elimination of plasma methotrexate in high-dose methotrexate therapy. *Br J Clin Pharmacol.* 2009; 67:44–49. [PubMed: 19076159]
19. Hiwase DK, Eadie L, Saunders V, Hughes T, White DL. Proton pump inhibitors augment nilotinib and dasatinib mediated Bcr-Abl kinase inhibition. *Blood.* 2010; 116:1626. abstr 3991.

Fig.

Steady-state C_{min} in newly diagnosed patients treated with nilotinib 300 mg twice daily (A, C) or 400 mg twice daily (B, D) according to concurrent PPI or H2 blocker use.

^aCimetidine and ranitidine were excluded from the H2 blocker group in C and D

Table 1
Concurrent use of PPI or H2 blockers with nilotinib

	ENESTnd: newly diagnosed CML-CP			Study CAMN107A2101: imatinib-resistant or - intolerant CML-CP
Patients, n (%)	Nilotinib 300 mg BID (n = 243)	Nilotinib 400 mg BID (n = 249)	Both arms combined (n = 492)	CML-CP patients (n = 256)
No PPI or H2 blocker	180 (74.1)	193 (77.5)	373 (75.8)	170 (66.4)
Concurrent PPI for any time period	48 (19.8)	39 (15.7)	87(17.7)	77 (30.1)
Concurrent H2 blocker for any time period	27 (11.1)	22 (8.8)	49 (10.0)	17 (6.6)
Concurrent PPI or H2 blocker for any time period ^a	63 (25.9)	56 (22.5)	119 (24.2)	86 (33.6)
Concurrent PPI or H2 blocker for any time period (excluding cimetidine and ranitidine)	49 (20.2)	45 (18.1)	94 (19.1)	77 (30.1)
Concurrent PPI or H2 blocker for >50% of time ^a	26 (10.7)	20 (8.0)	46 (9.3)	59 (23.0)

BID twice daily; *CML-CP* chronic myeloid leukemia in chronic phase; *ENESTnd* Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients; *H2 blocker* histamine 2 receptor antagonists; *PPI* proton pump inhibitor

^aIncluded all H2 blockers identified

Table 2
Efficacy of nilotinib according to concurrent PPI or H2 blocker use

	I: Patients with no PPI or H2 blocker	II: Patients with concurrent PPI or H2 blocker for any duration ^a	III: Patients with concurrent PPI or H2 blocker for any duration (excluding cimetidine and ranitidine)	IV: Patients with concurrent PPI or H2 blocker for >50% of time	P value
ENESTnd: newly diagnosed CML-CP; MMR at 12 months (%)					
Nilotinib 300 mg BID	75 of 180 (41.7)	32 of 63 (50.8)	27 of 49 (55.1)	13 of 26 (50.0)	
Nilotinib 400 mg BID	78 of 193 (40.4)	27 of 56 (48.2)	20 of 45 (44.4)	12 of 20 (60.0)	
Both arms combined	153 of 373 (41.0)	59 of 119 (49.6)	47 of 94 (50.0)	25 of 46 (54.3)	0.13 ^b
Study CAMN107A2101: imatinib-resistant or -intolerant CML-CP					
MCyR by 12 months (%)	98 of 170 (57.6)	55 of 86 (64.0)	48 of 77 (62.3)	34 of 59 (57.6)	0.40 ^b
CCyR by 12 months (%)	65 of 170 (38.2)	39 of 86 (45.3)	35 of 77 (45.5)	23 of 59 (39.0)	0.34 ^b
					0.89 ^c

BID twice daily; *CCyR* complete cytogenetic response; *CML-CP* chronic myeloid leukemia in chronic phase; *ENESTnd* Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients; *H2 blocker* histamine 2 receptor antagonists; *MCyR* major cytogenetic response; *MMR* major molecular response; *PPI* proton pump inhibitor

^aIncluded all H2 blockers identified

^bChi-square test comparing II versus I

^cChi-square test comparing patients who had responses and received PPI or H2 blockers for >50% of the time on nilotinib versus patients who had responses but received PPI or H2 blockers for <50% of the time