Outcome of 82 chronic myeloid leukemia patients treated with nilotinib or dasatinib after failure of two prior tyrosine kinase inhibitors

Antonella Russo Rossi,[1] Massimo Breccia,[2] Elisabetta Abruzzese,[3] Fausto Castagnetti,[4] Luigiana Luciano,[5] Antonella Gozzini,[6] Mario Annunziata,[7] Bruno Martino,[8] Fabio Stagno,[9] Francesco Cavazzini,[10] Mario Tiribelli,[11] Giuseppe Visani,[12] Patrizia Pregno,[13] Pellegrino Musto,[14] Carmen Fava,[15] Nicola Sgherza,[1] Francesco Albano,[1] Gianantonio Rosti,[4] Giuliana Alimena,[2] and Giorgina Specchia[1]

[1]Ematologia con Trapianto, Università degli Studi di Bari "Aldo Moro", Bari; [2]Dipartimento di Biotecnologie Cellulari ed Ematologia, Università "La Sapienza", Roma; [3]Ematologia, Ospedale Sant'Eugenio, Roma; [4]Ematologia, Università di Bologna; [5]Ematologia, Università "Federico II", Napoli, Italy; [6]Ematologia, Università di Firenze; [7]Ematologia, Ospedale Cardarelli, Napoli; [8]Ematologia, Ospedale Bianchi-Melacrino-Morelli, Reggio Calabria; [9]Ematologia, Ospedale Ferrarotto, Catania; [10]Ematologia, Università di Ferrara; [11]Ematologia, Università di Udine; [12]Ematologia, Ospedale San Salvatore, Pesaro; [13]Ematologia, Ospedale San Giovanni Battista, Torino; [14]Dipartimento Ematologia e Trapianto Cellule Staminali, Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture; and [15]Ematologia, Polo Universitario ASO San Luigi Gonzaga, Orbassano, Italy

ABSTRACT

There have been few reports of a response to dasatinib or nilotinib after failure of two prior sequential tyrosine kinase inhibitors. We report the outcome of 82 chronic phase patients who received nilotinib or dasatinib as third-line alternative tyrosine kinase inhibitor therapy. Thirty-four patients failed to respond to nilotinib and were started on dasatinib as third-line tyrosine kinase inhibitor therapy while 48 patients were switched to nilotinib after dasatinib failure. Overall, we obtained a cytogenetic response in 32 of 82 patients and major molecular response in 13 patients; disease progression occurred in 12 patients. At last follow up, 70 patients (85.4%) were alive with a median overall survival of 46 months. Our results show that third-line tyrosine kinase inhibitor therapy in chronic myeloid leukemia patients after failure of two prior sequential tyrosine kinase inhibitors may induce a response that, in some instances, could prolong overall survival and affect event-free survival.

Introduction

The advent of tyrosine kinase inhibitors (TKIs) has dramatically changed the outcome of chronic myeloid leukemia (CML). Imatinib has induced rates of over 80% complete cytogenetic response (CCyR) and 70% major molecular response (MMR).[1,2] Despite this success, about 20% of patients demonstrate primary or acquired resistance to this drug.[3,4] Several mechanisms may contribute to this phenomenon,[5-7] but the onset of mutations has been reported as a major determinant of resistance.[8-10] With 2nd generation TKIs (2nd TKIs), dasatinib or nilotinib, it has been demonstrated that approximately 50% of patients failing to respond to previous treatments can be rescued.[11-15] Few reports have described the outcome of patients who, after failing to respond to 2nd TKIs, were treated with third-line TKI.[8,11] We report the long-term outcome of a large series of CML patients who received dasatinib or nilotinib as third-line TKI therapy.

Design and Methods

Patients being sequentially treated with 3 TKIs were recruited by 18 Italian centers. Patients were strictly monitored according to European Leukemia Net (ELN) recommendations[5] at different time points. In cases of resistance, mutational analysis was performed with direct sequencing and DHPLC, before starting 2nd TKIs. Patients were switched to dasatinib or nilotinib in cases of failure or severe intolerance and responses were monitored according to 2009 ELN provisional criteria for 2nd TKI after imatinib resistance. Intolerance was defined as grade 3-4 hematologic or non-hematologic toxicity or persistent grade 2, despite best supportive therapies. Response criteria were defined according to ELN recommendations[5] (Table 1). Univariate and multivariate logistical models were used to evaluate the effects of variables (gender, age, CyR to imatinib, etc.) on CyR to third-line TKI therapy (Table 2). Covariates in the multivariate logistical regression models were chosen by stepwise-with-backward elimination variable selection procedures. *P* values less than 0.05 were considered statistically significant. The analyses were performed using SPSS software for Windows, version 13.0. Survival probabilities were estimated by the Kaplan-Meier method, and compared by the log rank test.

Ethics

This study was approved by the Ethical Committee at the Policlinico of Bari, Italy.

Results and Discussion

A total of 82 patients were recruited and treated sequentially with TKIs: median age was 62 years (range 33-85); 29 were male and 53 female. Sixty-two patients (75.6%) had received

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Correspondence: g.specchia@ematba.uniba.it

prior interferon-alpha before starting on imatinib; 20 patients (24.4%) received imatinib as first-line therapy. Sokal's risk evaluation at baseline showed that 27% of patients were low, 25% intermediate and 48% high risk. No patient had undergone allogeneic transplant (HSCT) before receiving TKIs. At the start of imatinib, all patients were in chronic phase (CP). Median time on imatinib therapy was 45 months (range 4-101), and median imatinib dose was 400 mg/day. Ten patients received high-dose imatinib for resistance to standard dosage. Best overall response to imatinib was MMR in 6 patients (7.3%), CCyR in 19 patients (23.2%), partial CyR (PCyR) in 21 patients (25.6%), minor CyR (mCyR) in 10 patients (12.2%), only complete hematologic response (CHR) without any CyR in 21 patients (25.6%). No response (NR) was observed in 5 patients (6.1%). Imatinib was discontinued in 74 patients (90.2%) due to resistance and in 8 (9.8%) due to intolerance.

Table 1. Baseline patients' characteristics.*

Parameter	GROUP A	GROUP B
Number of patients	34	48
Median age (years; range)	60 (43-85)	60 (33-80)
Gender (male/female)	9/25	20/28
Sokal Risk		
Low	9	14
Intermediate	8	11
High	17	23
Interferon-alpha therapy		
Yes	28	34
No	6	14
Best response to imatinib		
NR	2	3
CHR	9	12
mCyR	4	6
PCyR	9	12
CCyR	9	10
MMR	1	5
Reasons for discontinuation of imatinib		
Resistance	32	42
Intolerance	2	6
Stage at the time of starting second-line TKI therapy		
CP	30	42
AP	2	5
BC	2	1
Response to second-line TKI therapy		
NR	8	8
CHR	8	13
mCyR	6	3
PCyR	5	4
CCyR	7	9
MMR	–	11
Reasons for failure of second-line TKI therapy		
Resistance	17	24
Intolerance	14	24
Both	3	–
Disease stage at the time of starting third-line TKI		
CP	30	38
AP	1	8
BC	3	2

*CP: chronic phase; AP: accelerated phase; BP: blastic phase; NR: no response; mCyR: minor cytogenetic response; PCyR: partial cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response.

Responses to second-line TKIs

Thirty-four patients received nilotinib as second-line TKI therapy at a starting dose of 400 mg BID (Group A): 30 of 34 (88.2%) patients were in CP, 2 (5.9%) in accelerated phase, and 2 (5.9%) in blastic phase (BP). Thirty-two patients were switched to nilotinib due to resistance, and 2 to intolerance to imatinib. Median time of imatinib treatment before the switch was 47 months (range 6-67). Mutational screening at baseline, performed in 19 patients, revealed that 10 patients had developed mutations before starting treatment, probably due to the long duration of the disease (*Online Supplementary Table S1*). The most frequent mutations detected were F317L(2), A269S, H295P+F311L+Y320H, M244V, M351T+F359C, E255K(2), Y253H, S417F. Twenty-four patients (70.6%) received no other treatment before starting nilotinib, whereas 7 patients (20.6%) received hydroxyurea (HU), 2 patients (5.9%) high-dose imatinib, one patient (2.9%) HSCT. Best response to nilotinib was CCyR in 7 patients (20.6%), PCyR in 5 patients (14.8%), mCyR in 6 patients (17.6%), CHR in 8 patients (23.5%), and NR in 8 patients (23.5%). None of the treated patients obtained MMR. Median time on second-line nilotinib was 30 months (range 1-36).

Forty-eight patients were treated with dasatinib as second-line TKI therapy (Group B): 42 of 48 (87.5%) patients were in CP, 5 (10.4%) in accelerated phase, one (2.1%) in BP. Twenty patients (41.7%) received a starting dose of 70 mg BID, the remaining patients received doses of 50 mg BID or 100 mg QD. In 35 patients (73%), no interval treatment was given between the discontinuation of imatinib and the start of dasatinib, whereas one patient received IFNα, one chemotherapy (cytosine-arabinoside), 3 patients high-dose imatinib, 6 patients HU, and 2 patients underwent HSCT. Ten patients (29.4%) were found to have mutations before starting dasatinib: the most common mutations were M244V(3), F359V(2)+E450G, N322D+K400E+E409G+K467R, T315A+P309R, M351K, M351V, D276G. Forty-two patients were considered resistant and 6 intolerant to imatinib. Best response to dasatinib included MMR in 11 patients (22.9%), CCyR in 9 patients (18.7%), PCyR in 4 patients (8.3%), mCyR in 3 patients (6.3%), only CHR in 13 patients (27.1%), and no response in 8 patients (16.7%). Median time on second-line dasatinib was 13 months (range 4-59) (Table 1).

Efficacy and safety of third-line TKIs

Group A was made up of 34 patients: 30 patients were in CP (88.2%), one patient in accelerated phase (2.9%) and 3 patients in BP (8.8%). These patients were started on dasatinib as third-line TKI therapy. Fourteen patients (41%) were switched to dasatinib for intolerance; 17 (50%) patients were considered resistant to nilotinib: 8 patients were screened for mutations and these were found in 4 of them (T315I, F317L, F359C, E255V). Three patients were considered both intolerant and resistant: none of these patients presented mutations. Eighteen patients were evaluated for mutational screening at the time of the switch and mutations were identified in 8: 5 new mutations (F359V, T315I, F359V, Y253H (2)+F359V) and 3 confirmed mutations (A269S, F317L, F359C).

Group B was made up 48 patients: 38 patients in CP (79%), 8 patients in accelerated phase (16.6%) and 2 patients in BP (4%). These patients were started on nilotinib as third-line TKI therapy. Twenty-four patients

(50%) were considered intolerant to dasatinib: among these, mutations were found in 6 of 18 patients tested (F317L(2), M244V(2), L387M, M351T). Twenty-four patients were considered resistant to dasatinib and switched to nilotinib: 8 of 18 patients tested presented a mutation at the time of the switch (F317L(3), M244V(2), M318T, T315I, G250E). Twenty-four patients were taken off because of intolerance (most common side effects were pleural effusion and thrombocytopenia). Overall, best response to third-line TKI treatment was MMR in 13 patients (15.9%), CCyR in 14 patients (17.1%), PCyR in 12 patients (14.6%), mCyR in 6 patients (7.3%), only CHR in 26 patients (31.7%). Twelve patients (14.6%) did not achieve any response. In Group A, treatment was discontinued in 14 of 34 (41.2%) patients because of toxicity. In Group B, 24 patients of 48 (50%) experienced severe toxicity requiring treatment discontinuation. Two new mutations (F317L, E255V) emerged with dasatinib and 2 new mutations (Y253H, G250E) with nilotinib as third-line TKI therapy; 9 patients (26%) in group A and 3 patients (21%) in group B had disease transformation. After a median follow up of 14 months (range 2-37), 50 patients (48 CP and 2 accelerated phase) are still in treatment (33 patients with nilotinib and 17 with dasatinib). At last follow up, 70 patients (85.4%) were still alive with a median overall survival of 46 months (range 15-300). Twelve patients died (14.6%) of disease progression associated with T315I development.

Univariate and multivariate analyses were performed to identify predictive factors associated with the achievement of CyR to third-line TKI therapy (Table 2). Patients who did achieve a CyR on imatinib or with low and intermediate Sokal risk had a higher probability of achieving CyR with third-line TKI therapy (P<0.001). The presence of a mutation before starting a third-line TKI therapy did not affect the response. During follow up, 13 (15.9%) patients failed to respond to third-line TKI therapy and 12 (14.6%) died of disease progression. The 30-month probabilities of event-free survival (EFS) and overall survival (OS) were 76.4% in CP patients and 16.5% in AP (advanced phase: accelerated phase+BP) (P<0.001) and 98.5% in CP patients and 76.1% in AP (P<0.001), respectively (Figure 1A and B).

Although the use of imatinib has improved cytogenetic and molecular responses as compared to previously available therapies,[16,17] approximately 30-50% of patients did not achieve a CCyR within 12 months of therapy. Furthermore, IRIS results at 8-year follow up showed that 17% of patients had primary resistance and 15% lost a previously obtained CyR.[18,19] From sponsored trials, 40-50% of resistant patients can be rescued by 2nd generation TKIs, but patients who failed to respond to first-line are

Table 2. Univariate and multivariate regression analysis of factors affecting CyR to third-line TKIs*.

	Univariate logistical model			Multivariate logistical model§		
	Coefficient (β)	SD	P	Coefficient (β)	SD	P
Age <65 *vs.* ≥65 years	-0.011	0.158	0.943	‡	‡	‡
Gender Male *vs.* female	-0.787	0.168	0.640	‡	‡	‡
Sokal risk High *vs.* intermediate/low	-0.390	0.139	0.006	-0.448	0.0952	<.001
CyR to imatinib (at least mCyR)	0.572	0.189	0.003	0.552	0.0952	<.001
CyR to second TKI	0.0724	0.197	0.714	‡	‡	‡
Mutations	0.675	0.190	0.50	‡	‡	‡
Resistance	-0.346	0.194	0.079	‡	‡	‡
Intolerance	-0.356	0.187	0.60	‡	‡	

**CyR: cytogenetic response; mCyR: minor cytogenetic response; TKI: tyrosine kinase inhibitor; §model with variables selected by stepwise procedure; ‡variables deleted by stepwise procedure.*

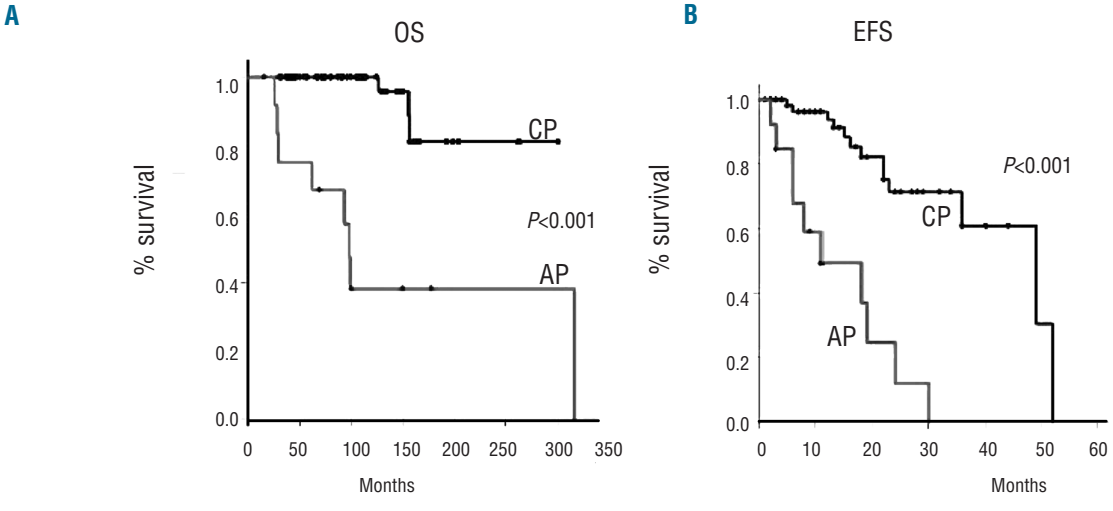

Figure 1. Kaplan-Meier estimates for overall survival (OS) and event-free survival (EFS) in CML patients treated with third-line tyrosine kinase inhibitor therapy after failure of two prior sequential tyrosine kinase inhibitors. (A) OS of patients in chronic phase (CP) and advanced phase (AP: accelerated phase + blastic phase). The 30-month probabilities of OS were 98.5% in CP patients and 76.1% in AP (P<0.001). (B) EFS of patients in chronic phase (CP) and advanced phase (AP: accelerated phase + blastic phase). The 30-month probabilities of EFS were 76.4% in CP patients and 16.5% in AP (P<0.001).

at risk of losing the response also to second-line TKIs.[14,15] Tam *et al*. suggested that patients treated with 2nd TKIs had a higher progression rate if they did not obtain an MCyR within 12 months or were completely Ph^+ after 3 or 6 months.[4] Limited data have been published on the use of nilotinib or dasatinib after failure of two prior TKIs. Garg *et al*. reported 48 CML patients, 25 in CP and 23 in accelerated phase/BP (34 treated with dasatinib after imatinib/nilotinib failure and 14 with nilotinib after imatinib/dasatinib failure):[8] with third-line therapy, CP patients obtained MMR (5 patients) and CCyR (3 patients) as best response, the latter showing a median duration of 16 months. Even in advanced phases of disease, in terms of best response, 2 patients achieved MMR and 3 patients a CCyR. After a median follow up of 16 months, 13 patients were still continuing therapy and median EFS was 13 months. Quintas-Cardama and colleagues reported a single center experience of the use of dasatinib after failure of previous imatinib and nilotinib in 23 patients (19 patients in advanced phases), obtaining a CCyR rate of 30%.[11] Nilotinib was reported to overcome imatinib and dasatinib failure in 67 patients (27 CP, 15 accelerated phase and 25 BP): in CP patients the MCyR rate was 32%, whereas 23% of the accelerated phase patients returned to CP. Of 20 evaluable BP patients, 15% had a CHR and 5% returned to CP.[20] The results of the present study, confirm the impressive efficacy of both agents used as rescue therapy after failure of two prior TKIs, but highlighted some important issues. Firstly, the median duration of responses obtained with a third-line TKI therapy is not so long. Secondly, as shown also in our experience, the frequency of emerging mutations in patients treated sequentially with different TKIs is higher. In fact, two new mutations with an IC50 of more than 3 nM (F317L, E255V) emerged with dasatinib and two new mutations with an IC50 of more than 150 nM (Y253H, G250E) emerged with nilotinib as third-line TKI therapy, reflecting the use of sequential TKI therapy. In our experience, approximately 14% of patients died of progression associated with the onset of a T315I; as also reported elsewhere, sequential treatment with several TKIs could cause selection of this mutation.[21-23] We observed a similar toxicity rate in third-line TKI therapy with both agents (41.2% discontinuation of nilotinib and 50% of dasatinib). However, in spite of the presence of side effects, 70 of 82 patients are still alive with a median OS of 46 months. Among patients who failed to respond to dasatinib or nilotinib or with a T315I mutation, recent results showed that ponatinib, a 3rd generation TKI, could have anti-leukemic activity and may also act as a bridge to HSCT.[24] In conclusion, our results show that a third-line TKI therapy, after failure of two prior TKIs, might induce a response that, although transient in some instances, could prolong OS and, in particular, delay the onset of events. Third-line TKI therapy could be a valid therapeutic option for some categories of patients not eligible for HSCT, such as elderly patients with comorbidities.

Appendix

All these authors also contributed to this study. Mario Delia (Ematologia con Trapianto, Università degli Studi di Bari "Aldo Moro", Italy), Paolo Avanzini (Servizio di Ematolgia, Arcispedale S.M.Nuova, Reggio Emilia, Italy), Ferdinando Porretto (Ematologia, Ospedale La Maddalena, Palermo, Italy), Diamante Turri (Ematologia, Ospedale Cervello, Palermo, Italy).

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Authorship and Disclosures

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