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Dasatinib tyrosine kinase inhibitor as second and third line therapy in chronic myeloid leukemia: outcome of a Nepalese study

Nora Ranjitkar Manandhar,[1] Gyan Krishna Kayastha,[2] Paras Kumar Acharya[3]

[1]Assistant Professor, [2]Professor, Department of Internal Medicine, Patan Academy of Health Sciences, Lalitpur, Nepal

Correspondence
Dr. Nora Ranjitkar Manandhar
Department of Internal Medicine, Patan Hospital, Patan Academy of Health Sciences, Lalitpur, Nepal
Email: noraranjitkar@pahs.edu.np

Peer Reviewers

Assist. Prof. Dr. Ashis Shrestha
Patan Hospital, PAHS

Prof. Dr. Jay N Shah
Patan Hospital, PAHS

ABSTRACT

Introductions: Dasatinib is indicated as a first line, second line and third line tyrosine kinase inhibitor (TKI) in chronic myeloid leukemia (CML). In our center it is used as a second line or third line therapy in BCR-ABL gene positive CML.

Methods: It is a retrospective observational therapy done from June 2015 to May 2018. The purpose of the study is to see the response rates using the second line and third line dasatinib after failing or not tolerating imatinib alone or following a sequential therapy with imatinib and nilotinib.

Results: A total of 31 (male 56.3%) patients were included in our study. In eighteen patients it was used as a second line TKI and in 13 a third line TKI. Complete Hematologic Response (CHR) was achieved in 93.55%. Best optimal responses were 46.66% and 61.53% in second and third line dasatinib respectively. Major Molecular Response (MMR) was achieved in 35.71% (26.66% and 46.14% in second line and third line dasatinib respectively). For both the groups, the overall survival was 92% and 94 % at 20 months and the event free survival was 70% at 10 months.

Conclusions: Dasatinib is effective in achieving MMR and inducing survival benefit in the patients who failed imatinib alone and imatinib and nilotinib.

Keywords: chronic myeloid leukemia, dasatinib, imatinib failure or intolerance, imatinib and nilotinib failure or intolerance

Resistance or intolerance to imatinib-treated chronic myeloid leukemia (CML) patients are seen in 33% and yet, 33% of the patients never achieve complete cytogenetic response (CCyR).[1,2] Clinical resistance to imatinib is divided into either primary if the patient showed lack of efficacy from the initiation of the therapy, or secondary if resistance develops after initial response,[1,3] characterized by loss of Major Cytogenetic Response (MCyR).[6] Resistance is further classified as hematologic (absence of normalization of blood counts), cytogenetic (persistence of Ph+ cells) and molecular (persistence of BCR-ABL transcripts by the Reverse Polymerase Chain Reaction 'RTPCR'[6] as per the National Comprehensive Cancer Network (NCCN) guidelines 2018.[1,6]

Resistance is considered if at three months, the BCR-ABL transcripts is >10% by Quantitative Polymerase Chain Reaction (QPCR) or, in absence of Partial Cytogenetic Response (PCyR), at six months. If the above response persists or there is a mutation that has known resistance to imatinib and at 12 months or later if the BCR-ABL transcript is >1% or presence of mutation.[1]

In this study, we have tried to report the response rates and the results using second generation Tyrosine Kinase Inhibitor (TKI) dasatinib as a second and third generation TKI, after failure or intolerance to imatinib alone and response rates in these patients who had failed or developed intolerance to the sequential use of imatinib and nilotinib following imatinib resistance.

Table 1. Definitions of the Accelerated Phase and Blast Phase as defined by the WHO guideline and definitions of the various responses[3,4,5,6]

Accelerated Phase	
Peripheral Blood Blast	>/=10% and =/< 19%,
Peripheral Blood Basophils	>20%
Platelet Count Unrelated to Therapy	</=100*109/L
Thrombocytosis	>1000*109
Increasing Spleen Size	
Cytogenetic Evidence of Clonal Evolution	
Blast Phase	
Peripheral White Blood Cells or of Nucleated Bone Marrow Cells	>/=20% blasts
Complete Hematologic Response	
Complete normalization of peripheral blood counts with absence of immature cells such as myelocytes, promyelocytes, or blasts in the peripheral blood	
Leukocyte Count	<10*109/L
Platelet Count	<450*109/L
Cytogenetic Response	
Complete Cytogenetic Response (CCyR)	no Ph positive metaphases
Partial Cytogenetic Response (PCyR)	1-35% Ph positive metaphases
Major Cytogenetis Response (MCyR)	0-35% Ph positive metaphases
Minor Cytogenetic Response (mCyR)	>35% Ph positive metaphases
Molecular Response	
Early Molecular Response (EMR)	BCR-ABL (IS) =/< 1-10% at 3 and 6 months
Major Molecular Response (MMR)	BCR-ABL (IS) =/< 0.1% or =/> 3 log reduction in BCR-ABL messenger ribonucleic acid (mRNA) from the standardized baseline
Complete Molecular Response or deep molecular response (CMR)	MR 4.5

METHODS

This was a cross-sectional study done at Patan Hospital in Nepal, on the patients who had been receiving dasatinib after developing resistance or showed intolerance to the first line TKI - imatinib and after failure or intolerance to second line TKI - nilotinib. All the charts of the patients who had received dasatinib were studied. The patients included were: BCR-ABL gene positive Chronic Myeloid Leukemia; patient with documented results complete blood count, cytogenetic tests, molecular tests; documentation of failure or intolerance to imatinib only and nilotinib. Patients who do not have the documented reports of the above tests were excluded. Data were collected from June 2015 to May 2018.

Baseline characteristics like name, age, sex, address, whether the patient received imatinib alone or was sequentially treated with imatinib and nilotinib and the median time taken were calculated. The phase (chronic, accelerated and blast phases, table 1) at which the various TKIs used were also noted. The mutational analyses were done by IRMA (Imatinib Resistance Mutation Analysis) and their results were also recorded. The best optimal response achieved (hematological, cytogenic and molecular, table 1) with imatinib and nilotinib were recorded and the reasons for stopping them and the phase at stopping them were also noted. Similarly, the best response achieved with the use of dasatinib and the final outcomes were documented. Optimal response was said to be present if there was at least early molecular response (EMR) at 3 to 6 months, at least a complete cytogenetic response at 6 months, and at least a major molecular response (MMR) at 12 months and thereafter. The response rates lying between the optimal and resistance are termed as warning responses. The response rates were evaluated as per the NCCN 2018 guidelines[1] for the management of Chronic Myeloid leukaemia.

The patient outcome was studied including the percentage of hematologic responses, cytogenetic responses and the molecular responses, mutations and outcomes; overall survival and, event free survival were calculated by using SPSS 20 software. The events were defined as the failure response, death, and loss to follow up.

RESULTS

A total of 32 patients were started on dasatinib as a second line or the third line TKI. One patient was excluded from the study as he was newly started with dasatinib and the reports were not available. So, the total of 31 patients were included with males 18 (58.06%). The median age of the patients was 45 years (range 15-80). One patient received hydroxyurea and another received hydroxyurea and interferon before being enrolled in our center.

Imatinib as a first line TKI: All of the 31 patients received imatinib as a first line of treatment, median time on imatinib was 47.5 months (range 1-159). At baseline, 30 (96.77%) patients were in the chronic phase and one (3.23%) in accelerate phase. The best responses achieved with imatinib were optimal response 12 (46.15%), warning and fail 14 (53.85%) data was not available in rest 5 patients. Four (12.9%) patients were taken off imatinib due to intolerance out of which three (75%) had optimal response as a best response and the response status of one patient was not known. Two out of those three patients later developed secondary resistance to imatinib. In the remaining 27 (87.09%) patients, imatinib was discontinued due to resistance.

Out of 29 patients whose latest response was failure 13 (41.93%) patients developed hematologic failure, two (6.45%) developed cytogenetic failure, 14 (45.16%) patients had a molecular failure, one (3.22%) patient had optimal response and data of one patient was not available but had maintained the CHR, (Table 2).

Mutational was performed in 27 (87.09%) patients. Mutation was seen in 15 (55.55%) patients when resistance was documented and it was not seen in 12 (44.44%). The presence of mutations associated with the strong resistance to imatinib like Y253H, G250E, and L248V were seen in 5 (33.33%) patients out of which four patients had primary resistance and one had secondary resistance (G250E). Mutations with intermediate resistance to imatinib M244V, H396R, F359V/C, L387M and M351T were seen in 9 (60%) patients. Out of which five (M244V-1, F359V-2, F359C-1 M351T-1) had a primary resistance two (L387M-1, F359V-1) had a secondary resistance to imatinib and in two (H396R) categorization was not done because of the missing data. Presence of E275K and A269S mutation conferred a primary and secondary resistance to imatinib respectively.

Mutations sensitive to dasatinib F359V, L387M, G250E, Y253H, M244V, H396R, M351T and intermediate sensitivity mutation E255V and F317L were found in our patients but the outcomes were varied, (Table 3).

Table 2. Patients characteristics before starting imatinib, dasatinib as a 2nd line TKI, nilotinib, dasatinib as a 3rd line TKI, the best responses achieved, results as per the latest reports and the reason for discontinuing it

TKI and Number of Patients	Imatinib n=31	Dasatinib 2nd line n=18	Nilotinib 2nd line n=13	Dasatinib 3rd line n=13
Stage at start of TKI				
Chronic Phase (CP)	30 (96.77%)	3 (16.66%)	5 (38.46%)	5 (38.46%)
Accelerated Phase (AP)	1 (3.22%)	1 (5.55%)	3 (23.07%)	4 (30.76%)
Blast Phase (BP)		1 (5.55%)	0	
Cytogenetic Failure		1 (5.55%)	1 (7.69%)	
Molecular Failure		10 (55.55%)	4 (30.76%)	3 (23.07%)
Complete Hematologic response (CHR)		1 (5.55%)	5 (38.46%)	4 (30.76%)
Major Molecular Response (MMR)				1 (7.69%)
Early Molecular Response (EMR)		1 (5.55%)		
Time on Months	47.5, (R 1-159)	9, (R 4.8-35.36)	24, (R 7.25-91.13)	11.6, (R 4.06-5.76)
Best Response				
CHR		18 (100%)		12 (92.30%)
Optimal	12/26 (46.15%)	7/15 (46.66%)	2 (15.38%)	8 (61.53%)
Warning	4 /26(15.38%)	7/15 (46.66%)	1 (7.69%)	2 (23.07%)
Failed	10/26 (38.46%)	1/15 (5.33%)	10 (76.92%)	2 (15.38%)
NA	5 (16.12%)	3/18 (16.66%)		
Latest Response				
CHR	7 (22.58%)	16 (88.88%)		12 (92.30%)
Molecular Test done in patients		15 (83.33%)		13 (100%)
Deep Molecular Response		2 (13.33%)		3 (15.38%)
MMR		2 (13.33%)		4 (30.76%)
Early MolecularResponse (EMR)	1 (3.22%)	2 (13.33%)		1 (7.7%)
Warning		3 (20%)		1 (7.7%)
Failed	29 (93.54%)	6 (40%)	13 (100%)	5 (38.46%)
NA		3 (16.66%)		0
Reason for discontinuation/starting				
Intolerance	4 (12.90%)	3 (16.66%)	1 (7.69%)	1 (7.69%)
Resistance	27 (87.09%)	15 (83.33%)	13 (100%)	13 (100%)
IRMA test done in	27 (87.09%)	14 (77.77%)		13 (100%)
Mutation seen	15 (55.55%)	5 (35.71%)		11 (84.61%)
Mutation not seen	12 (44.44%)	9 (64.28%)		2 (15.38%)

Dasatinib as a second line TKI: Eighteen patients received dasatinib as the second line therapy, median time 9 month (Range 4.8-35.36). At baseline 15 (83.33%) patients were resistant to imatinib. Rest three (16.66%) who had had intolerance to imatinib; one pulmonary stenosis suffered chest discomfort, another patient who had rheumatic heart disease developed pulmonary edema and yet another patient had sweet syndromes along with resistance to imatinib. The IRMA test of the patient with sweet syndrome showed L248V mutation. She did not achieve optimal response with dasatinib but she maintained CHR. The patient with pulmonary stenosis and rheumatic heart disease had optimal response as early molecular response (EMR) and complete hematologic response (CHR). Both of these patients achieved the deep molecular response (MR4) and major molecular response (MMR) respectively with dasatinib, (Table 3).

In 15 patients, five had hematologic failure, nine had molecular failure and one had cytogenetic failure. Altogether 14 (77.77%) patients underwent mutational analysis using IRMA. Mutations were observed in 5 (35.71%%) patients and not seen in 9 (64.28%). In four, it was not performed. CHR was achieved as the best response on those patients in whom mutation was seen. Reports of molecular test was available in 15 patients and in three it was not. Seven (46.66%) patients achieved the optimal response as the best response. Warning response was seen in seven (46.66%) patients as the best response. In one (6.66%) patient there was failed response. All three patients without molecular tests, they were able to achieve CHR.

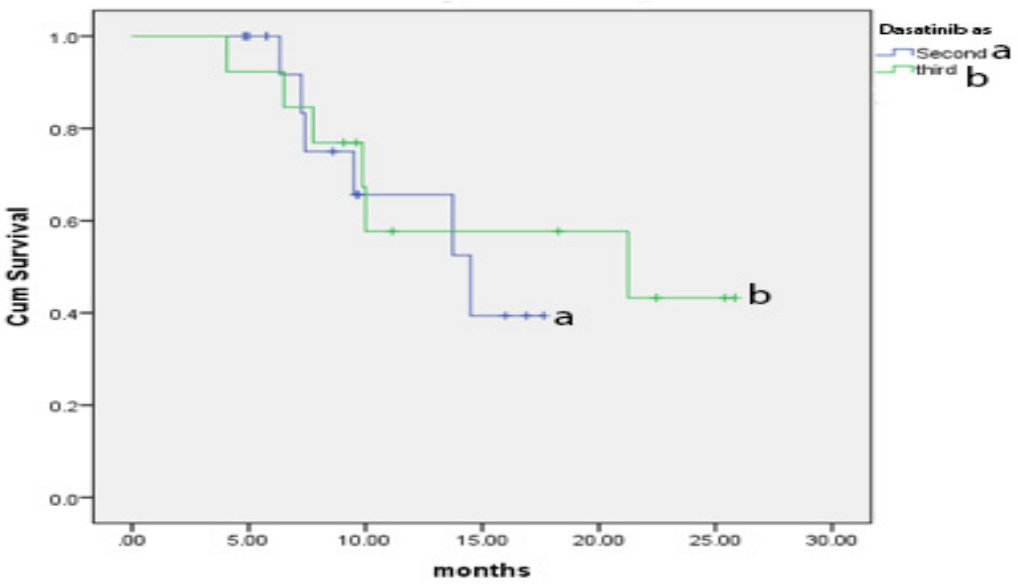
After dasatinib was used as second line, in total 16 (88.88%) patients were able to achieve CHR, and two (11.11%) patients progressed to hematologic resistance. Deep molecular response was achieved by two (13.33%) patients, major molecular response by two (13.33%), early molecular response by two (13.33%), warning by three (20%) and the resistance was observed in six (40%) patients.

Table 3. Showing the mutation status and response with second and third line dasatinib

SN	Mutation	Number	Failed HR	CHR	QPCR	MR4	MMR	EMR	Warn	Fail
Dasatinib as a Second line TKI										
1	Y253H	1	none	1	done		1			
2	G250E	1	AP	1	not done					
3	L248V	1	none	1	done					1
4	A269S	1	none	1	done					1
5	M244V	1	none	0	done					1
6	not seen	9	4	8		1	0	2	3	2
7	Not done	4	none	4	3	1	1			1
Dasatinib as a Third line TKI										
1	H396R	1	AP	1	done					1
2	Y253H	2	CP 1	2	2	1				1
3	F359V/C*#	5	CP2+AP2	5	5	0	3		1	1
4	L387M^	1	CP	1	done	1				
5	E255K/V^&	2	CP1	2	done	1		1		
6	E355G^	1	CP	1	done	1				
7	M351T&	1	none	1	done			1		
8	E275K*	1	CP	1	done		1			
9	M244V#	1	CP	1	done		1			
10	F317L	1	AP	0	done					1
11	not seen	2	CP1	2	done		1			1

Note: HR: Hematological Response, CHR: Complete Haematological Response, QPCR: Quantitative Polymerase Chain Reaction, MR4: Deep Molecular Response, MMR: Major Molecular Response, EMR: Early Molecular Response. #,^,&, * : mutations present in the same patient.

In three patients the molecular tests were not available but complete hematologic response was achieved. Thus, 26.66% of the patients were able to achieve at least an MMR. In the patients who had mutation, one patient was able to achieve MMR. The dasatinib sensitive mutation like Y253H, G250E and M244V were seen in three patients. One (M244V) (5.55%) had primary resistance and succumbed due to disease progression. IRMA analysis did not show mutations in nine (64.28%) patients, (Table 3).



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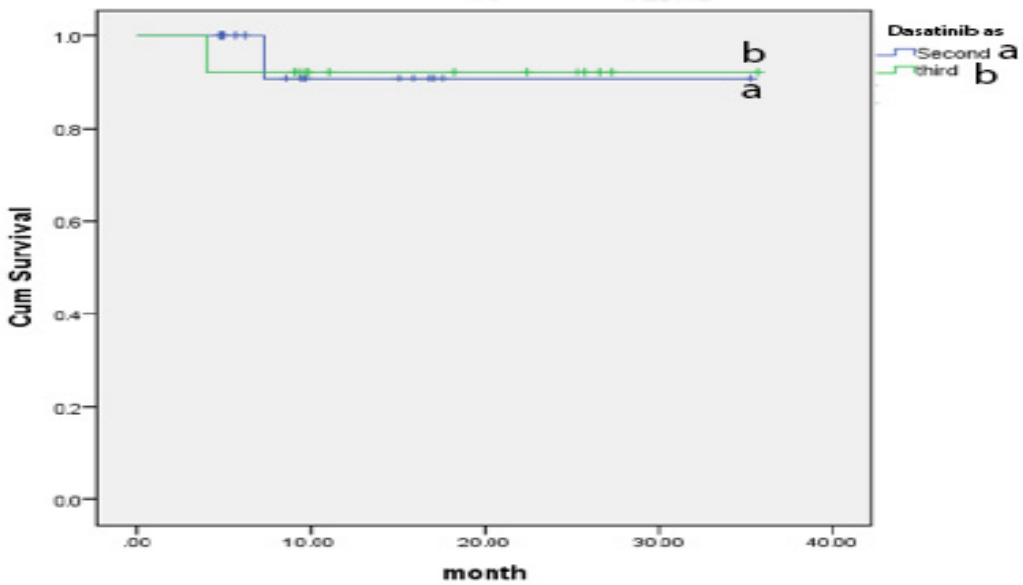
p= 0.6

Figure 1. Figure showing the event free survival curve, where death, failure and lost to follow up were taken as events in the groups using dasatinib as a second line or third line therapy



p=0.09

Figure 2. Kaplan Meier Curve showing overall survival in patients using 2nd line and 3rd line dasatinib

In four patients IRMA was not performed. One was able to achieve deep molecular response, one MMR and one had primary resistance to dasatinib. In the remaining one patient, the molecular tests were not performed but CHR was achieved. The event free survival was 70% at 10 months The median event free survival was 14 months. Overall survival was 92% at 20 months.

Dasatinib as a third line TKI: Dasatinib was used as a third line TKI in 13 patients median time 11.16 months, (Range 4.06-35.766 months). These patients received nilotinib after failing (12) or not tolerating (1) imatinib. The median duration on nilotinib was 24 months (R 7.25-91.13). One patient was switched to nilotinib as he had acute kidney injury following imatinib therapy. However, he needed to be changed to dasatinib as his kidney injury worsened with nilotinib too and he also had a prolonged QTc interval. He achieved the optimal responses as the best response with all three TKIs.

At base line, out of thirteen, nine (69.23%) patients had hematologic failure, 5 (55.55%) patients were in the chronic phase and 4 (44.44%) in the accelerated phase. Rest three (23.07%) patients had molecular failure but had maintained the complete hematologic response, and the last one (7.69%) patient had MMR.

All the patients underwent mutational study and mutation was seen in 11 (84.61%) and in 2 patients (15.38%) mutation was not detected.
Seven patients underwent IRMA test while on nilotinib. New mutation was seen in three patients, three had the same mutation as before and in one patient it was not present.
The best response as optimal response was achieved in 8 (61.53%), warning in 3(23.07%) and failed response in two (15.38%).

After using dasatinib as third line complete hematologic response was achieved in 12 (92.30%), deep molecular response was achieved in 2(15.38%), major molecular response in 4 (30.76%), early molecular response in 1 (7.7%), warning response in 1 (7.7%) and resistance was seen in 5 (38.46%) patients. Thus, a minimum of MMR was achieved in six (46.15%) of the patients. The commonest mutation was F359V/C (5/11), Out of these five patients, three patients (60%) achieving at least an MMR, one patient achieved EMR and another one patient developed resistance to dasatinib

In three patients, each one with H396R, Y253H and F359V mutations were associated with the primary resistance to dasatinib. Mutations Y253H, F359V, F359C, L387M, and M351T mutations were associated with good outcome, as all of them were associated with the optimal response. Out of seven patient having these mutations, two patients achieved deep molecular response, 3 achieving a major molecular response and one achieving an early molecular response. One patient however developed the warning response.

In two patients, the IRMA test did not show any mutation. Dasatinib as a third line TKI conferred MMR in one patient and in another there was a primary resistance.

In a patient who never achieved the optimal response with imatinib had E275K mutation. He was started on nilotinib wherein he had a hematologic failure with the rise in the pcr value and IRMA showed F359V mutation. He was thus put on dasatinib.

The patient who had primary resistances to imatinib and nilotinib had F359V mutation was started on dasatinib to which there was a good response initially but later developed a resistance. IRMA showed M244V mutation. He responded well to the dose escalation of dasatinib.

Overall, the event free survival was 70% at 10 months of starting dasatinib in this groups as shown in figure 1. The median event free survival was 22 months. The overall survival of the patients at 20 months was 94%, Fig 2.

DISCUSSIONS

In our study, best hematologic response as CHR was achieved in 100% and 92.30% with 2nd line and third line dasatinib respectively. It was maintained at 88.88% and 92.30% at the end of the study. In the study where dasatinib was used as the 2nd and 3rd line TKI, CHR was achieved in 28.57% and 70.58% respectively.[3] In the START C and START A trial where dasatinib was used in the CP and BP of CML CHR was achieved in 91% and 45% respectively.[7,8] Yet in another study by Brave et al. on dasatinib as a second line TKI, CHR was seen in 90%, 33% and 24% in CP, AP and BP respectively. It is evident that the patients who are at greater phase of CML had worse hematologic prognosis.[9] CHR achieved in these studies is comparable our study where all phases of CML were taken as a unit.

In our study we did not perform cytogenetic study but did the molecular test. Achievement of MMR is better than to achieving CCyR. Kantarjian, et al, in their study had shown that the patients who had CCyR, on follow up showed increase in RTPCR than that of MMR but they maintained CCyR [10] So, in our study, total MMR or higher response was achieved in 35.71% of patients who were on dasatinib. MMR was achieved in 26.66% and 46.15% of patients receiving 2nd line and 3rd line dasatinib respectively. In the study performed in the patients on second line and third line TKI, over all CCyR was achieved in 64.4% of the patients.[7] In another study the second line and third line dasatinib induced CCyR in 14.28% and 26.47% respectively. In the START- C trial, second line dasatinib was able to achieve MMR in 25% of the patients where as in START-A trial the second line dasatinib induced CCyR in 32% of the patients.[7,8] Similarly, in the START-R trial MMR of 29% was achieved with second line dasatinib where as in another study where dasatinib is used as a third line TK, I MMR was achieved in 19.2%.[11,12] Again, MMR of 11.76% was seen in the patients receiving third line TKI.[3] Over all the response rate is found to be comparable with the results of our study. In our study, EMR was seen in 13.33% and 7.7% in 2nd and 3rd line dasatinib respectively. It has been found that achievement of EMR to be associated with the improved progression free survival (PFS) and overall survival (OS), as PFS was 56% and 57% in patients EMR at three to six months in comparison to 21% and 14% in those who did not achieve EMR.[13]

Resistance to second line and third line dasatinib was 40% and 38.46% respectively, also seems to be comparable to that in the clinical trials. In the study on 2nd line and 3rd line dasatinib, resistance was seen in 35.57%.[14] In another study, the resistance to the 3rd line dasatinib was seen in 42%.[12] In a study using dasatinib as a 2nd line TKI primary resistance was seen in 28.57% of the patients but 64% of the patients eventually failed.[3] In the group using dasatinib as a third line TKI, primary resistance was encountered in 9%, and loss of CHR was seen in 18% of the patients and over all resistance was observed in 42%.[3]

Overall mortality rate in our study was 6.45%. Here, using dasatinib as a second line and third line TKI, mortality rate was 5.55% and 7.69% respectively. In other studies, mortality rates using 3rd line dasatinib was 37.5% and 34.6%.[3,12] In the study by Brave, et al., the mortality rate associated with the use of second line dasatinib was 2%. Thus, the mortality rate that occurred in our study does not seem to be higher than that of the other studies.

In our study, the use of both second line and third line dasatinib was able to achieve overall survival (OS) of 92% and 94% at 20 months respectively, and the event free survival (EFS) of 70% at 10 months. In the study by Garg et al, the event free survival was 55%, 30%, and 18% at 13 months in patients using dasatinib as a 3rd line TKI in CP, AP and BP respectively.[14] In the study by Santos, et al. the PFS and OS was observed in 90% at 6.7 months and 96% at 11.8 months respectively.[15] Similarly, in the seven year follow up study of dasatinib as a second line TKI, PFS and OS at year 2 and 7 were 70%, 94% and 42% , 65% respectively.[15] In the

study by Ibrahim et al, where dasatinib or nilotinib was used as the third line TKI, the 30 month OS was 72% in the patients who achieves CCyR and 20.4% in patients who did not achieve this response.[12] In the START C and START A trial PFS and OS was 90% and 96% at 15 months and 66% and 82% at 12 months respectively. [7,8]

In our study, the mutations in the patients, which were sensitive to the imatinib, nilotinib or dasatinib, the patients were still found not responding to treatment, calling into question the compliance to the medicines. It also explains the multimodal mechanisms for resistance, suggesting that mutation alone may not be the cause of the resistance to treatment.

L387M mutation was known to be sensitive to all 3 TKIs but our patient had this mutation when he had resistance to imatinib. He later developed resistance to nilotinib too and IRMA showed the new mutations E255K and E355G with the absence of the previous L387M mutation. As E255K mutation has the intermediate resistance to both dasatinib and nilotinib and E355G mutation was sensitive to dasatinib. Hence, dasatinib was started here.

Mutation with M351T was known to be sensitive to all 3 TKIs, but it was detected when our patient had a cytogenetic failure as well as a hematologic failure. This patient never had an optimal response to nilotinib but had always maintained a CHR and later showed molecular failure. A second new mutation E255V was seen which had an intermediate resistance to nilotinib and dasatinib.

Limitations of our study were small sample size, not enough to obtain their significance and all phases of CML were categorized as one. As discovered in the clinical trials response rates are lower for the patients in the blast phase or accelerated phase than in the chronic phase CML. We saw that our patients who were supposed to have a drug sensitive mutation had a resistance to the given TKI. In the ideal situation these patients would undergo assessment of plasma concentration of the drug to measure the drug compliance. This was not possible in our patients because the availability, validity and affordability of the tests.

CONCLUSIONS

In conclusion, dasatinib is effective in achieving response rates like CHR, MMR, EFS, and OS similar to those in the clinical trials in the patients who are resistant to or intolerant to imatinib alone or following sequential therapy with imatinib and nilotinib.

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REFERENCES

1. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. 2018. [internet]. Available from: https://www.nccn.org/professionals/default.aspx
2. Garg RJ, Kantarjian H, O'Brien S, et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. Blood. 2009;114:4361-8. DOI: https://doi.org/10.1182/blood-2009-05-221531

3. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase myeloid leukemia. N Engl J Med. 2003;348:994-1004. DOI: 10.1056/NEJMoa022457
4. Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med. 2003;349:1423-32. DOI: 10.1056/NEJMoa030513
5. Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World health organization classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2001.
6. Faderl S, Talpaz M, Estrov Z, Kantarjian M. Chronic myelogenous leukemia: biology and therapy. Ann Intern Med. 1999;131(3):207-19. DOI: 10.7326/0003-4819-131-3-199908030-00008
7. Apperley JF, Cortes JE, Kim DW, et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START a trial. J Clin Oncol 27(21):3472-9. DOI: 10.1200/JCO.2007.14.3339
8. Brave M, Goodman V, Kiminskas E, et al. Sprycel for chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to or intolerant to imatinib mesylate. Clin Cancer Res. 2008;14(2):352-9. DOI: 10.1158/1078-0432.CCR-07-4175
9. Kantarjian HM, Shan J, Jones D, et al. Significance of increasing levels of minimal residual disease in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in complete cytogenetic response. J Clin Oncol. 2009;27(22):3659-63. DOI: 10.1200/JCO.2008.18.6999
10. Kantarjian H, Pasquini R, Levy V, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily. Cancer. 2009;115(18):4136-47. DOI: https://doi.org/10.1002/cncr.24504
11. Ibrahim AR, Paliompeis C, Bua M, et al. Efficacy of tyrosine kinase inhibitors (TKIs) as third-line therapy in patients with chronic myeloid leukemia in chronic phase who have failed 2 prior lines of TKI therapy. Blood. 2010; 116(25):5497-500. DOI: https://doi.org/10.1182/blood-2010-06-291922
12. Shah NP, Rousselot P, Schiffer C, et al. Dasatinib in imatinib resistant or intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study of CA180-034. Am J Hematol. 2016;91(9):869-74. DOI: https://doi.org/10.1002/ajh.24423
13. Ibrahim AR, Clark RE, Holyoake TL, et al. Second-generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed. Haematologica. 2011;96(12):1779-82. DOI: 10.3324/haematol.2011.049759
14. Santos FP, Ravandi F. Advances in treatment of chronic myelogenous leukemia - new treatment options with tyrosine kinase inhibitors. Leuk Lymphoma. 2009;50(Sup 2):16-26. DOI: https://doi.org/10.3109/10428190903383427
15. Stone RM, Kantarjian HM, Baccarani M, et al. Efficacy of dasatinib in patients with chronic-phase chronic myelogenous leukemia with resistance or intolerance to imatinib: 2-year follow-up data from START-C (CA180-013). Blood. 2007;110(11):734. Abstract. Available from: http://www.bloodjournal.org/content/110/11/734