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CHRONIC MYELOID LEUKEMIA - CLINICAL

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(PB1943) MOLECULAR RESPONSE RATE AND SAFETY IN CHRONIC PHASE CHRONIC MYELOID LEUKEMIA PATIENTS WHO SWITCHED TO GENERIC IMATINIB: LONG-TERM ANALYSIS

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Background:

Imatinib has drastically changed the outcome of chronic myeloid leukemia (CML) patients. The last update of the IRIS trial has shown that the estimated OS rate at 10 years is 83.3% and data from registries have reported an OS approaching that of the general population. Since July 2017, a generic formulation of imatinib has been introduced in Italy for the treatment of patients with CML. The switch from branded to generic imatinib has been investigated in different countries in terms of efficacy and safety but with contrasting results.

Aims:

We analyzed the outcome of a large series of chronic phase (CP) CML patients treated consecutively at a single institution who switched from branded to generic imatinib in terms of molecular efficacy and safety profile.

Methods:

We retrospectively analyzed 168 CP-CML patients treated with branded imatinib for a median time of 12 years (range 1-16) who switched to only one generic formulation (Imatinib Accord). Physical examination and biochemical exams were carried out at least every 3 months and adverse events (AEs) were reported according to the CTCAE 5.0 scale. Molecular standardized RQ-PCR was performed every 3 months and responses were defined according to the ELN2013 recommendations.

Results:

Male and female patients were respectively 58% and 42%, with a median age of 52 years (range 18-82). The Sokal risk score was low/intermediate/high in 63%, 33% and 4% of cases, respectively. Median duration of generic imatinib treatment was 25.5 months (range 4-30). Twenty-seven % of patients were in MR3 and 73% in deep molecular response (MR4-4.5) at the time of switch. After 30 months of treatment with generic imatinib, 143 patients were evaluable for response: 27/143 (18.9%) and 116/143 (81.1%) patients were respectively in MR3 and MR4-4.5. Comparing the degree of response with the best molecular response reported with branded imatinib, we observed that 83.2% of patients maintained a stable response, 9.7% improved the degree of response and 6.5% had a molecular fluctuation from MR4-4.5 to MR3. Only 1 patient lost the MR3 response and no patient required a switch to another TKI for inefficacy. In terms of safety, 34/168 patients (20%) reported new or worsening side effects (15% grade 3, 74% grade 2, 11% grade 1).The most common were dyspepsia in 32.3% of patients, muscle cramps in 25%, conjunctival hyperemia in 18%, diarrhea in 15%, skin rash in 9%, arthralgia in 9% and elevated creatinine levels in 3%. Only 2 patients reverted to branded imatinib due to toxicity (1 developed gynecomastia and salivar gland hypertrophy and the other due to persistent gastrointestinal symptoms). Overall, 22 patients (13%) discontinued generic imatinib treatment for intolerance (n=2), treatment-free remission attempt (n=18) and due to other causes not related to treatment (1 patient for a relapse of an endometrial cancer and 1 for a non-related CML death).

Summary/Conclusion:

Our data show that the switch to a generic imatinib is associated to a persistent efficacy, although some patients experience new side effects. Long-term evaluation of tolerability is suggested when switching to a generic imatinib in order to reduce the impact on quality of life and consequent non-adherence to treatment.

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(PB1944) HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA WHO DISCONTINUED TREATMENT

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Background:

Approximately 50% of patients with chronic myeloid leukemia (CML) who discontinue treatment will remain in treatment free remission (TFR) for a long duration of time. It is widely assumed that treatment discontinuation improves patients' quality of life (QOL). However, outside clinical trials this assumption has not been systematically studied so far.

Aims:

Compare the QOL of patients with CML in TFR with that of patients matched by age and disease duration on treatment, using patient reported outcomes (PROs) questionnaires.

Methods:

This is a nationwide study of patients with CML including patients who are on TKI treatment and those in treatment free remission (TFR). This study is a joint initiative of the Israeli CML patients' organization and the Institute of Hematology at the Davidoff Cancer Center, Rabin Medical Center. The study was approved by the local Institutional Review Board in each hospital. Participants completed a computerized form that included validated questionnaires by the European Organization for Research and Treatment of Cancer (EORTC). The questionnaires included 30 core questionnaire items (QLQ-C30), a supplementary EORTC CML-specific 24 questionnaire items (QLQ-CML24) and other questions regarding QOL, which were added by the researchers. Demographics, disease and treatment related items including the use of analgesics and cannabis were also included. The EORTC questioners are composed of functional, symptom and global health/QOL scales/items. All scales and single-item measures range in score from 0 to 100. While a high scale score represents a high functional status and a high QOL, a high score for symptoms correlates with high symptom burden. Patients in TFR were matched by age (± 4 years) and time since diagnosis (± 1 year) to patients that were on treatment.

Results:

22 CML patients in TFR for at least 3 months (median: 16.5 months, range 3 to 57 months) were enrolled and completed the questionnaires. For each of these patients we matched between 1 to 11 patients of similar age group and disease duration that were on treatment. Overall the results of 80 patients (22 in TFR and a control group of 58 on treatment) are presented herein. Patients in the control group received imatinib (n = 40, 69%), dasatinib (n = 12, 21%) or nilotinib (n = 6, 10%). The median age at diagnosis was 67 (range: 37 to 84) years and time since diagnosis of CML ranged between 3 to 46 (median: 11) months. Patient's characteristics including gender distribution, family status, level of education and religion were similar in both groups.

The symptom burden during the last week of patients in TFR was lower. They reported significantly less episodes of nausea (P = 0.012), and had increased appetite (P = 0.01). The improved symptom profile was associated with reduced use of cannabis (P = 0.05) but similar use of painkillers (P = 0.6). Nevertheless, the physical, cognitive, emotional and social functions were similar across groups.

Summary/Conclusion:

Patients in TFR have improved symptom profile. However, symptom relief was not translated into improved physical cognitive emotional or social functions.

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(PB1945) DISCONTINUATION OF TYROSINE KINASE INHIBITOR (TKI) THERAPY IN CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE (CML-CP) IN US CLINICAL PRACTICE AFTER GUIDELINE UPDATES

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Background:

NCCN CML practice guidelines were updated in 11/2016 and in 9/2019 to include considerations for discontinuation of TKI therapy in patients (pts) with CML-CP.

Aims:

This study characterized TKI discontinuation practices in the US after these updates and drew parallels with a similar study conducted prior to these guideline updates (Ritchie et al. *Leuk Lymphoma*. 2019).

Methods:

Pt charts of adult CML-CP pts with TKI discontinuation (1/2017-12/2018) outside a clinical trial after achieving an adequate response were abstracted (11/2019-12/2019) via an online case report form by US oncologists/hematologists. Physicians' assessment of adequate response (TKI duration, molecular response [MR], MR duration) and relapse were described.

Results:

61 physicians (academic: 43%; community-based practices: 57%) contributed 153 pt charts. Most physicians were from large practices (57%), had >10 years (y) experience since completing subspecialty training (59%), and treated a median of 30 CML pts in the last 2y; 56% did not have access to precise molecular response monitoring for BCR-ABL of ≥4.5 log when attempting TKI discontinuation. Pts with TKI discontinuation had mean age 56 years, were mostly male (60%), white (69%), and had TKI discontinued in first-line (96%). Most common reasons for TKI discontinuation were pt request (54%) and adverse events (18%), besides achieving an adequate response. Physicians' assessment of adequate response for TKI discontinuation are reported in the **Table**. 21% of pts (academic: 12%; community: 30%) relapsed after TKI discontinuation (treatment-free remission [TFR] failure; 66% relapsed within 1y).

Before TKI discontinuation		**Overall (N = 153)**	**Academic (N = 77)**	**Community (N = 76)**
TKI therapy duration	<1y	20%	17%	17%
	1 - <2y	15%	17%	13%
	2 - <3y	14%	9%	20%
	≥3y	50%	57%	43%
PCR (BCR-ABL1/ABL1) MR	≤MR3	23%	21%	25%
	MR4	38%	31%	45%
	MR4.5	39%	48%	30%
MR duration	≤1y	48%	36%	61%
	2y	21%	25%	17%
	≥3y	31%	39%	22%

Summary/Conclusion:

Although NCCN CML practice guidelines provide guidance for discontinuation of TKI therapy, there remains heterogeneity in US practice and TKI discontinuation is predominantly attempted in first-line (similar to Ritchie et al. 2019). TKI discontinuation is being practiced without adequate sensitive tools mandated by practice guidelines to monitor response. Broader application of practice guidelines for optimal TKI therapy discontinuation in CML-CP pts is needed, particularly in community-based practices, to improve long-term TFR rates.

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(PB1946) THE PREVALENCE OF SECONDARY MALIGNANCIES AMONG 234 PATIENTS WITH CHRONIC MYELOID LEUKEMIA TREATED WITH TYROSINE KINASE INHIBITORS- SINGLE CENTER REPORT

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Background:

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder resulting from the formation of BCR-ABL fusion oncogene, which is constitutively active. The data about the prevalence of other secondary malignancies during treatment with Tyrosine Kinase Inhibitors (TKIs) among those patients are limited.

Aims:

This study sought to assess the incidence of secondary malignancies and describe baseline characteristics of CML patients treated with TKIs in single institution.

Methods:

The retrospective analysis of 234 patients from the Department of Hematology, Jagiellonian University Medical College suffering from CML treated with TKIs between 2009 and 2019 was performed. Demographic data and treatment details were analyzed. Statistical analysis was performed with StatSoft Statistica 12.

Results:

The study included 234 (female-47.9%) patients, in median age of 61 years (IQR 53-71). Median follow-up time was 81 months (IQR 30-138). 122 patients (52,1%) were treated with one TKI, 79 (33,8%) with two TKIs, 25 patients (10,7%)- three TKIs, 7 (3%)- four TKIs and 1 patient (0,4%) with five TKIs. Secondary malignancies were observed in 13 patients (5,6%): ovarian cancer (3 cases), uterine cancer, breast cancer (2 cases each), prostate cancer, thyroid cancer, rectal cancer, colon cancer, GIST and basal cell carcinoma (1 case each). Major molecular response (MMR) was achieved by 10 patients (77%) with secondary malignancies. There was no statistically significant difference between the frequency of secondary malignancies and number of TKIs used in therapy or MMR status. 4 patients were diagnosed with secondary malignancy before the onset of TKI treatment, 9 patients after TKI was introduced. Median time from the initiation of the TKI treatment to

secondary malignancy diagnosis was 80 months. None of the patients had neoplasm before CML diagnosis.

Summary/Conclusion:

This study did not reveal statistically significant difference between the number of TKIs used in therapy, MMR status achieved and the frequency of secondary malignancies among CML patients. Our study showed that female reproductive system cancers were the most common ones among consecutive patients.

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(PB1947) CHRONIC MYELOID LEUKEMIA IN ADOLESCENTS AND YOUNG ADULTS: DIFFERENCES WITH OTHER AGE GROUPS IN A MULTICENTRIC COHORT FROM ARGENTINA.

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Background:

International literature suggests that adolescents and young adults (AYA) with Chronic Myeloid Leukemia (CML) have a more aggressive disease at diagnosis, with lower treatment response rates and no impact in overall survival (OS). This age group constitutes a population at risk, with poor quality of life related to psychosocial sphere, long-term adverse effects of tyrosine kinase inhibitors (TKIs) and poor adherence. Few prospective studies deepen these findings, so research is needed to validate specific diagnostic, follow-up and treatment approaches for this subgroup of CML patients. **Aims:** To compare the clinical presentation, response to treatment and outcome of AYA patients (P) with CML with other age groups. **Methods:** Retrospective, descriptive, multicentric study based on data obtained from medical records of CML P diagnosed and/or treated between January 2000 and February 2020. Three cohorts studied: AYA (15-39 years (yrs)), adults (40 -60 yrs) and P over 60 yrs. Statistical analysis: Kruskal-Wallis and Chi square. Survival analysis: Kaplan-Meier/Log-rank test (p=0.05). **Results:** 655 CML P were registered. Median follow-up 72 months (RIQ: 29-133 months). Mean age at diagnosis: 44 years (range 15-85/SD 16.3), male 54% (357/655), CML phase at diagnosis: 95.5% (625/655) chronic (CP), 2% (13/655) accelerated (AP) and 2.5% (17/655) blast crisis (BC). Overall progression 12% (81/655), median time to progression 18 months (RIQ: 3–41). Overall mortality rate: 14% (92/655). The distribution in three cohorts was: AYA 44% (289/655), adults 37% (244/655) and P over 60 yrs 19% (122/655). Description of clinical presentation, treatment and outcomes by age group are shown in tables. No significant difference in overall response rates to TKIs. No significant difference in EFS and PFS. Mutations were detected in 56 patients (8.5%>56/655): AYA: 9% (27/289)-16/27 with T315I mutation. Adults: 9% (22/244)–7/22 with T315I. P over 60 yrs: 5.7% (7/122)-1/7 with T315I.

Table 1. Epidemiology and clinical presentation by age group (n=655).

		15-39 yrs (n: 289)	40-60yrs (n: 244)	>60 yrs (n: 122)	p
Mean age (yrs)		28.7	49.6	68.3	
Male		59% (173/289)	52% (126/244)	47% (58/122)	
CML phase at diagnosis	CP	96.1% (278/289)	95% (232/244)	94% (115/122)	
	AP	1% (3/289)	2.5% (6/244)	3.3% (4/122)	
	BC	2.7 % (8/289)	2.5% (6/244)	2.5% (3/122)	
Hemoglobin (gr/dl)#		10,8	11,3	11,8	**0.0026**
White blood cell count(/mm3)#		160.800	135.400	100.900	**0.2**
Platelet count (/mm3)#		543.000	624.000	534.000	0.81
Splenomegaly#		75% (134/180)	71% (96/134)	54% (37/68)	**0.001**
Spleen cm below costal margin#		8	6.5	3.2	**0.001**
Blasts (%)#		3	4	3	0.34
Basophils (%)#		2	3	3.8	**0.003**
Sokal Score*	· Low	66% (152/231)	61%(115/188)	22% (23/103)	0.0001
	· Intermediate	18% (41/231)	23% (44/188)	49% (51/103)	
	· High	16% (38/231)	15% (29/188)	28% (29/103)	

Clinical presentation of P diagnosed in CP (data available in 62% (382/625) of CP P)
* Data available in 83% (522/625) of CP P

Table 2. Need of subsequent TKI lines, progression, death and cause of death by age group (n= 655).

		15-39 yrs (n: 289)	40-60 yrs (n: 244)	>60 yrs (n: 122)	p
Second line		37% (107/289)	43% (106/244)	27% (34/122)	0.63
Third line		16% (46/289)	14% (35/244)	8% (7/122)	0.33
Fourth line		7% (20/289)	5% (15/244)	0	**0.02**
Progression		**12% (34/289)**	**14% (34/244)**	**10% (13/122)**	
Median time to progresion (months)		11 (RIQ 2,6-33)	22 (RIQ 2,8-41)	24 (RIQ 8,4-70)	
Mortality		**11% (31/289)**	**14% (35/244)**	**21% (26/122)**	
Cause of death	Progression	77% (24)	60% (21)	38% (10)	
	Treatment complications	3% (1)	8,5% (3)	12% (3)	
	Not related to CML	20% (6)	31% (11)	50% (13)	

Summary/Conclusion:

Taking into account that P included in this study are not correlative, the considerable percentage of AYA in a disease that is typically diagnosed around the age of 60 underlies the need for local registries in the country. We observe similar results to those reported in the international literature in terms of lower hemoglobin level, higher WBC count and greater splenic size at diagnosis in AYA CML P being the three variables statistically significant. AYA in this Argentinian cohort show more frequent need of subsequet lines of therapy. The lack of clinical data at diagnosis (near 40%) may limit the analysis by subgroups. We do not report significant difference in EFS, PFS or response rates. However we emphasize that, regardless of age, the high rate of events, progression and death related to CML (especially in AYA) highlights the importance of identifying key factors to optimize disease management in this special population given the well-known prognosis of CML in the TKI era, highlighting therapeutic adherence as the variable of great influence.

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(PB1948) FIVE YEARS OF EXPERIENCE OF BCR-ABL TESTING IN THE EVALUATION OF NON-LYMPHOCYTIC LEUKOCYTOSIS

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Background:

Evaluation of non-lymphocytic leukocytosis often includes BCR-ABL testing, a specific finding for chronic myelogenous leukemia (CML). The etiologies of non-lymphocytic leukocytosis are numerous, and CML is a rare disease with an annual incidence of 1-2 cases per 100,000 individuals. Further study is needed to identify patients with non-lymphocytic leukocytosis who are most likely to benefit from BCR-ABL testing.

Aims:

This study aims to improve utilization of BCR-ABL testing by comparing clinical characteristics of patients diagnosed with CML to those without CML.

Methods:

This retrospective study was approved by the Mayo Clinic Institutional Review Board. Eligible patients included those who had BCR-ABL testing (polymerase chain reaction and fluorescent in situ hybridization) for the evaluation of non-lymphocytic leukocytosis from January 1st, 2014 to December 31st, 2018. Patients with known CML were excluded. Complete blood counts were performed on the Sysmex XN-1000™ and Sysmex XE-5000™. White blood cell (WBC) differential counts were performed by automated and/or manual methods. Data collected from the medical records included demographics, duration of leukocytosis, presence or absence of splenomegaly (as documented by imaging and/or physical exam documentation), and comorbid medical conditions.

Results:

826 patients (56% female) met eligibility criteria. Median (range) age was 59 years (18 to 95). Median WBC was 14.5 x 10^9/L (9.7 to 746.5 x 10^9/L). 131 patients (16%) were diagnosed with CML. Patients with CML had a median WBC of 74.2 x 10^9/L (11.3 to 746.5 x 10^9/L), median neutrophil count of 50.4 x 10^9/L (6.9 to 408.8 x 10^9/L), and median basophil count of 1.3 x 10^9/L (0.0 to 54.5 x 10^9/L). The sensitivity and specificity of basophilia for CML was 87% (95% confidence interval [CI]: 80-92%) and 62% (95% CI: 59-66%) respectively. The sensitivity and specificity of peripheral blood myeloid

precursors (metamyelocytes, myelocytes, and/or promyelocytes) for CML was 86% (95% CI: 79-92%) and 85% (95% CI: 82-87%). The sensitivity and specificity of an absolute neutrophil count ≥8.0 x 10^9/L was 99% (95% CI: 95-100%) and 33% (95% CI: 30-37%). Splenomegaly was not sensitive (42%), however specific (86%) for the diagnosis of CML. The duration of leukocytosis prior to testing was not associated with a diagnosis of CML (261 days for CML vs. 402 days for non-CML, p=0.07).

Table 1. Laboratory and Clinical Findings in the Evaluation for CML

	Sensitivity	Specificity	LR (+)[1]	LR (-)[2]
Absolute Neutrophil count ≥8.0 x 10^9/L	99.2% CI 95.5-100%	33.4% CI 29.8-37.0%	1.49	0.02
Basophilia	87.0% CI 80.0-92.3%	62.3% CI 58.6-65.9%	2.31	0.21
Myeloid Precursors	86.3% CI 79.2-91.7%	84.9% CI 82.0-87.5%	5.71	0.16
Basophilia and Myeloid Precursors	76.3% CI 68.1-83.3%	92.4% CI 90.1-94.2%	10.01	0.26
Splenomegaly	42.2% CI 33.5-51.2%	86.3% CI 83.4-88.9%	3.08	0.67

[1]Positive Likelihood Ratio

[2]Negative Likelihood Ratio

Summary/Conclusion:

To our knowledge, this is the largest study evaluating patients with non-lymphocytic leukocytosis undergoing BCR-ABL testing. This study does not support testing for BCR-ABL on the basis of duration of leukocytosis alone, but rather endorses review of the WBC differential prior to testing. Screening patients for an absolute neutrophil count ≥8.0 x 10^9/L and the presence of basophilia and/or circulating myeloid precursors should be considered to increase the diagnostic yield of BCR-ABL testing. The presence of basophilia was not specific for a diagnosis of CML, encouraging further study into the differential diagnosis of basophilia in this patient population.

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(PB1949) EVALUATION OF LABORATORY AND INSTRUMENTAL INDICATORS OF HEART FAILURE IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA UNDERGOING TREATMENT WITH TYROSINE KINASE INHIBITORS

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Background:

In the tyrosine kinase inhibitors (TKI) era the survival rate of patients (pts) with chronic myeloid leukemia (CML) has become significantly higher. In these conditions, comorbidity and cardiovascular diseases are in particular of importance. There is an evidence in literature of the TKI's effect on the left ventricular (LV) systolic function, which can potentially increase the risk of congestive heart failure (CHF).

Aims:

To assess laboratory and instrumental myocardial condition in pts with CML.

Methods:

The study included 131 pts with CML (46% were male). The median age was 49 (20-76) years. Imatinib, Nilotinib, Dasatinib and Bozutinib were ever used in treatment of 97%,55%,29% and 11% pts, respectively; 1,2,3 and 4 TKI were used in 29%, 47%, 18%, and 7% of pts. The average duration of TKI therapy was 86 months. All pts were assessed for the presence of CHF manifestations by questioning, physical examination and application of questionnaires. Two-dimensional transthoracic echocardiography (Echo) was performed in all pts. The level of cardiomarkers NT-proBNP and ST2 (suppression of tumourigenicity 2 factor) were evaluated in 52 (40%) and 26 (20%) pts. All tests were performed before switching to another TKI and dynamically thereafter.

Results:

Clinical manifestations of CHF were present in 14 (10%) pts. According to Echo data, the average LV ejection fraction (LVEF) was 62%. It was reduced (<50%) in only 2 pts, including one of them with clinically CHF. A high value of NT-proBNP (>300pg/ml) was registered in 12/52 (23%) pts, including 3 pts with clinically CHF. In the group of pts with high and normal levels of NT-proBNP the average WBC level was 45*10^9/l and 18*10^9/l ($p<0.05$), and the average hemoglobin level (Hb) was 106 g/l and 119 g/l ($p<0.05$), respectively.

Anemia 1-3 grades and/or absolute leukocytosis were observed in 10/12 (83%) pts with high NT-proBNP level. Normalization of the NT-proBNP level was observed in 8 out of 10 evaluated pts after 3-6 months of switching to another TKI. It was correlated with normalization of both Hb and WBC level in 6 pts. In another 2 pts without anemia, normalization of NT-proBNP was clearly correlated with a decrease in WBC level. The ST2 cardio marker was elevated in 5 (19%) pts. At the same time both NT-proBNP and ST2 were elevated in only 1 pt. None of the pts with anemia and/or leukocytosis had an increase in ST2 level.

Summary/Conclusion:

In majority of pts with CML undergoing long-term treatment with TKIs LV systolic function remained intact. The level of NT-proBNP, unlike ST2, correlated with the level of Hb and/or WBC. It appears that the relevance of NT-proBNP as a marker of LV dysfunction in CML pts is limited. The clinical significance of the ST2 marker should be studied in a larger cohort of CML pts.

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(PB1950) ANALYSIS OF TKI DISCONTINUATION IN CML PATIENTS AS PART OF DAILY CLINICAL PRACTICE IN HOSPITALS OF THE CANARY ISLANDS, SPAIN

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Background:

Recent clinical trials have demonstrated that approximately 50% of patients with CML treated during several years with TKIs and that reach a deep molecular response (MR) can successfully maintain remission after the discontinuation of TKI treatment, known as treatment free remission (TFR). However, the factors influencing the discontinuation success still remain unknown.

Aims:

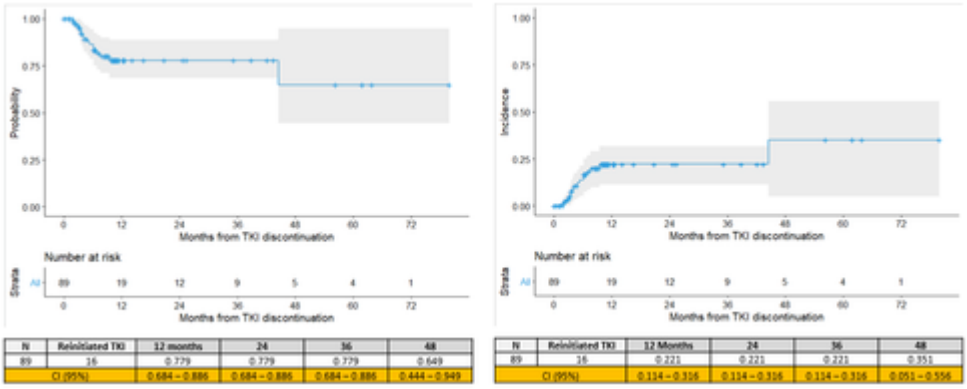
This retrospective study by the Canarian Group on CML collected data of CML patients who had discontinued ITK treatment as part of daily clinical practice in Canary Islands, Spain, and compared with published studies.

Methods:

We studied a total of 89 patients who discontinued treatment between 2012 and 2020 from Canary Island; discontinuation was programmed in 80 patients (89.9%) and 9 discontinued for other reasons (3 for adverse effects, 3 voluntarily, 1 for pregnancy and 2 for comorbidity). In our series, 51.69% of patients discontinued imatinib and 48.31% discontinued second-generation TKIs. Mean age of discontinuation was 59.27 years; 45 were men; Sokal score was low or intermediate in 92.05% of patients. Mean time of treatment before discontinuation was 109.41 months, with a mean follow up after discontinuation of 12.65 months. In 17 patients, TKI dose before discontinuation was below the recommended dose.

Results:

The TFR rate at 12 months was 77.9% (95% CI: 68.4%>88.6%) (Fig.1). Of the patients who lose MMR, 83.3% did so in the first six months after discontinuation, two of them did not reinitiate treatment, one for pregnancy and one due to the patient's decision. Among those who restarted TKI treatment, 95.45% reached MMR in a mean time of 2.47 months, and all of them were in MR4 or better. For our cohort, a duration of TKI treatment less than 59.4 months (p= 0.0078) and of MR4 less than 51.5 months (p= 0.0004), calculated as prognostic cut-offs from ROC analysis, were associated with a higher risk of molecular relapse (Cox regression analysis). Neither sex, age, Sokal risk score nor withdrawal syndrome had prognostic impact. A BCR-ABL1/ABL1 > 0.00086 prior to discontinuation was marginally associated with higher risk of molecular relapse (p=0.08). We found no differences between the TFR rates of patients who received a reduced TKI dose before discontinuation. Interestingly, we didn't find any significance (p=0.34, Kaplan survival analysis) between the TFR of patients who discontinued imatinib (n=46) versus second-generation TKI (n=43). For patients who discontinued imatinib, age < 47.43 years was a prognostic variable for TFR (p=0.022) as was a BCR-ABL1/ABL1 > 0.00086 prior to discontinuation (p=0.011). In contrast, for second-generation TKIs, a duration of RM4 > 52 months (p=0.01) and duration of TKI treatment > 59.38 months (p=0.012) were associated with TFR. However, there were statistically significant differences between the duration of TKI treatment (average 133.57 vs 83.57 months) and duration of MR4 prior to discontinuation (average 101.42 versus 61.02 months) of patients who received imatinib vs those who received second-generation TKI respectively.



Summary/Conclusion:

The results from our cohort suggest that a duration of TKI treatment > 59.4 months and remaining in MR4 > 51.5 months prior to discontinuation are good prognostic markers for TFR, in agreement with the data published by the Spanish Group on CML (GELMC). Therefore, a duration of Deep MR of two years prior to discontinuation, as currently recommended by the experts and NCCN, may be insufficient. In addition, age and BCR-ABL1/ABL1 levels can be important TFR prognostic factors in patients under Imatinib treatment

CML AdvocatesNetwork

(PB1951) DOSE REDUCTION OF SECOND GENERATION TYROSINE KINASE INHIBITORS IN CHRONIC MYELOID LEUKEMIA PATIENTS WITH MAJOR AND DEEP MOLECULAR RESPONSE

Margarita Gurianova*[1], Oleg Shukhov[1], Ekaterina Chelysheva[1], Anna Petrova[1], Anastasia Bykova[1], Irina Nemchenko[1], Olga Pospelova[1], Anna Turkina[1]
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Background:

Therapy with tyrosine kinase inhibitors (TKI) allows to achieve a deep molecular response (DMR) in 60-70% of patients (pts) with chronic myeloid leukemia (CML). According to the current guidelines CML pts receive a long-term treatment with TKI in standard doses. The frequently observed adverse effects (AE) of TKI therapy are mostly dose-dependent. A new treatment approach with TKI use in reduced dose is desirable for the CML patients with AE or with a high risk of AE occurrence.

Aims:

To evaluate the stability of major molecular response (MMR) in CML pts with MMR and DMR after dose reduction of second generation TKI (2G-TKI).

Methods: A retrospective study included 36 CML pts with MMR or DMR and treated with reduced dose of 2G-TKI. CML in chronic and accelerated phase at diagnosis was in 34 and 2 pts respectively. Median (Me) age at dose reduction was 47 years (range 22-71), males 44%. Four (11%) pts received 2G-TKI in 1st-line, 30 (83%) pts in 2nd-line and 2 (6%) pts in 3rd-line therapy. Me duration of TKI therapy was 42.5 months (mo, range 19-201), MMR was in 7(19%) pts, DMR - in 29(81%) pts, Me duration of MMR (including DMR) was 21.5 mo (range 1-51) at the time of dose reduction. AE was the reason for dose reduction in 21 pts (58%), other reasons in 15 (42%) pts (prevention of late AE, patient's request, insufficient drug supply). The dose reduction of nilotinib and dasatinib was done in 28(78%) and 8 (22%) pts accordingly. Initial daily doses of nilotinib were 800 mg, 600 mg, and 400 mg in 18(64%), 8(28%) and 2 (7%) pts, respectively. The doses of nilotinib were reduced to 600 mg, 400 mg, 300 mg, and 200 mg in 1(4%), 21(75%), 2(7%) and 4 (14%) pts, respectively. The initial daily doses of dasatinib were 140 mg in 1(12.5%) and 100 mg in 7(87.5%) pts, and doses of dasatinib were reduced to 70 mg and 50 mg in 2 (25%) and 6 (75%) pts, respectively. Molecular relapse after dose reduction was defined as loss of MMR (BCR-ABL IS >0.1%). Molecular relapse-free survival (MRFS) after 2G-TKI dose reduction was evaluated by Kaplan-Mayer method. The censoring was based on the date of the last BCR-ABL evaluation, discontinuation of therapy or TKI dose increase without MMR loss.

Results:

Me follow-up after 2G-TKI dose reduction was 13 mo (range 3-51). MRFS at 12 mo was 90% (CI 79%>100%), 96% (CI 89% -100%) and 64% (CI 23-100%) in the total cohort of pts, DMR and MMR cohort, respectively (Fig.1). The loss of MMR occurred in 3 pts with MMR lasting for 3, 6 and 8 mo at the time of dose reduction. No MMR loss was observed in pts with MMR duration > 12 mo. MMR was achieved in all pts after the standard dose therapy was resumed. Three pts with initial MMR achieved a DMR after 2G-TKI dose reduction. The toxicity after dose reduction was resolved in 19(90%) of 21 pts with the previously observed AE, no new or unexpected AE were observed after dose reduction. Eight (22%) pts with sustained DMR discontinued treatment after dose reduction phase.

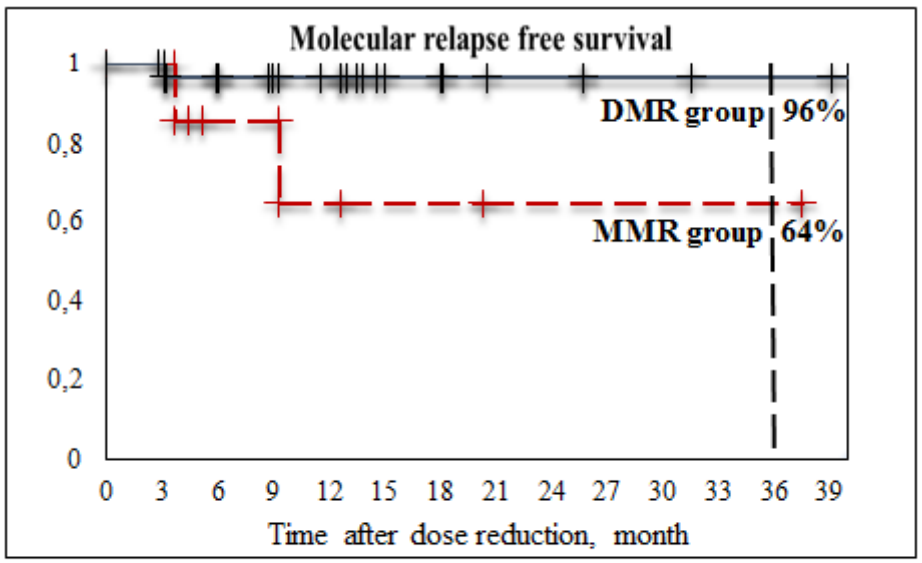

Figure 1. Molecular relapse-free survival in CML patients after 2G-TKI dose reduction

Summary/Conclusion:

The dose reduction of 2G-TKI in CML pts with MMR and DMR allows to reduce the drug toxicities and to prevent the potential AE of TKI therapy. At least one year of MMR duration on standard dose is desirable before dose reduction. Dose reduction can also be a cost-effective approach to therapy.

CML AdvocatesNetwork

(PB1952) ENDOCRINE EFFECTS INDUCED BY TYROSINE KINASE INHIBITORS DURING THE TREATMENT OF CHRONIC MYELOID LEUKEMIA

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Background:

BCR-ABL tyrosine kinase inhibitors (TKIs) developed in Chronic Myeloid Leukemia (CML) have transformed the prognosis of this disease. They cause a wide range of side effects, including endocrine (mostly thyroid) effects. They modify thyroid function by causing hypo- or hyperthyroidism.

Aims:

To evaluate the effect of tyrosine kinase inhibitor (Imatinib, Dasatinib, Nilotinib) on the endocrine system and evaluate the management of this adverse event.

Methods:

We evaluated the effect of the 3 TKIs available in our department (Imatib, Dasatinib and Nillotinib), on thyroid function. This is a prospective study, gathering 24 patients with CML, treated by these different TKIs, in hematology consultation. Thyroid function tests including TSH, FT4, FT3, Anti-TPO (anti-thyroid peroxidase), and anti-thyroglobulin (Anti-Tg) were evaluated at the start and during follow-up with TKI.

Results:

The median age is 53 years [39 - 72], sex ratio = 1. 96% of patients were in the chronic phase. The prognostic classification of our serie is as follows according to the Sokal score: low risk (n = 5), intermediate (n = 5) and high (n = 12). Before TKI treatment, 22 patients (92%) had normal thyroid function. Two thyroidectomy patients supplemented with levothyroxine and treated with Imatib also received higher doses of levothyroxine due to worsened hypothyroidism. Thyroid function disorders occurred in patients receiving Imatib in 25%, Dasatinib in 29% and Nilotinib in 46%. Thyroid dysfunction was variable, subclinical in 71% of patients and clinical in 7, one of whom presented with a thyrotoxic coma. The various anomalies are represented in the majority of cases by hypothyroidism, 02 cases of hyperthyroidism, an arachnoidocele and appearance of thyroiditis. The thyroid effects did not require discontinuation of ITK therapy, with the exception of one patient, whose week-long interruption followed by gradual resumption of ITK (Nilotinib). Thyroid abnormalities resolved spontaneously in 6 patients, while substitution with deficient hormone (Levotyroxine) involved 17 patients.

Summary/Conclusion:

The pathophysiological mechanisms are still uncertain and vary according to the molecules. Detecting TKI-induced thyroid dysfunction requires systematic monitoring of thyroid function and may require treatment.

Prescribing treatment with ITK requires carrying out a thyroid hormone assessment (TSH) before starting it, but also during treatment and after stopping it. Prospective trials are necessary to define the incidence of thyroid dysfunction during treatment with these different ITKs.

CML AdvocatesNetwork

(PB1953) CHARACTERISTICS OF CML PATIENTS WITH PRIMARY AND SECONDARY FAILURE TO STANDARD DOSE OF IMATINIB IN THE FIRST LINE AND THEIR RESPONSE TO SECOND TPEAT М EHT LINE

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Background:

Introduction of TKIs into the treatment of CML significantly altered the natural course of the disease and increased 10-year survival by 60%. Imatinib mesylate is the first approved TKI that has revolutionized the treatment of this disease and in many countries is used as the first line treatment. Recent data have shown that after a 10-year follow-up on imatinib only half of pts remain on treatment, not only because of primary resistance but also due to loss of response (secondary failure).

Aims:

of our study were to analyze differences in characteristics between groups of pts with primary or secondary failure on standard-dose of imatinib in first line treatment (TL) and their response to the secondary treatment (imatinib escalated dose 800mg or nilotinib 800mg dose).

Methods:

Our retrospective study included 92 consecutive patients with chronic phase of CML who experienced primary or secondary failure to first line imatinib treatment at standard 400mg dose. Three patients with adverse drug reactions were excluded from the analysis. All patients were diagnosed and treated at university Clinic for Hematology, CCS. The 2013 ELN criteria were used to evaluate the treatment response.

Results:

After a median follow-up of 83 months (range 12-276), 35 pts (39%) had a primary while 54 patients (61%) had a secondary failure to standard imatinib dose. Patients with primary failure had significantly higher leukocyte counts (p=0.019), percentage of blasts in peripheral blood (p=0.019), and spleen size (p=0.004) compared to pts with secondary failure. According to Sokal model, 54.3% of pts with primary failure and 18.5% of pts with secondary failure belonged to high risk-group. According to multivariate Cox regression analysis, Sokal model was the most important predictor of primary failure relative to the development of secondary failure in imatinib-treated patients (HR 2.221; 95% CI 1.353-3.647; p=0,028). Patients with primary failure have

shorter survival than pts with secondary failure. The presence of initial additional cytogenetic aberrations as well as their occurrence during follow-up did not differ significantly between groups of patients with primary and secondary failure. In second TL, administration of an escalated dose of imatinib resulted in a higher percentage of complete cytogenetic response (CCgR) in primary failure while nilotinib administration was efficient in secondary failure. A total of 20.2% of patients failed treatment with second TL. Patients treated with imatinib escalation had twice higher incidence of subjective, objective, and laboratory complications then pts with nilotinib. Significant factor in predicting response to nilotinib as second TL was percentage of Ph+cells in the moment of changing therapy. According to multivariate Cox regression analysis, Hammersmith score only showed significance in the prediction of achievment of CgR to nilotinib treatment in second TL (HR 2.977; 95%CI 1.061-8.538; p=0,001). The Hammersmith score showed significant correlation with achievement of CCgR, DMR as well as with survival in nilotinib treated pts in second TL.

Summary/Conclusion:

Our results showed that pts in the high-risk Sokal group had a threefold higher incidence of primary then secondary failure during imatinib treatment in first TL. Patients with primary failure during standard-dose of imatinib have a significantly lower percentage of CCgR achievement and higher incidence of treatment failure during second TL. Failure to second TL had 1/5 of pts and those pts need newer generation of TKIs for treatment.

CML AdvocatesNetwork

(PB1954) GENERIC IMATINIB TREATMENT IN CML. ALGERIAN STUDY OVER 12 YEARS (2007 - 2018): ABOUT 881 CASES, GAT-LMC

DJOUADI LAHLOU KHEDIDJA*[1], Bouchakour yamina[2], ABAD MOHAND TAYEB[3], TAOUSSI SOUAD[3], BRADAI MOHAMED[3], OUCHENANE ZAHRA[4], SIDIMANSOUR NOUREDDINE[4], ABDENNEBI NAIMA[5], AHMED NACER REDHOUANE[5], HAMLADJI ROSE MARIE[5], ENTASOLTAN BADRA[6], BEKADJA AMINE[6], TOUIL FATMA ZOHRA[7], HAMDI SELMA[7], BOUGHRIRA SORAYA[8], GRIFI FATIHA[8], SABER CHERIF DALILA[1], TAIBI KARIMA[9], TOUHAMI ELHADJ[9], SAIDI DJAMEL[9], LAKHDARI NOUREDDINE[10], KERRAR CHAHIRA[11], BOUDJERRA NADIA[11], MEHALHAL MALIKA[12], BENZINEB BRAHIM[13], MESLI NAIMA[13], GHERRAS SABIHA[14], AIT ALI HOCINE[14], OUADDAH FOUZIA[15], ZOUAOUI ZAHIA[15], LAMARA DJAAFAR[16], BENDJABALLAH BASSIMA[16], YACHEKOUR TOUFIK[17], BACHIRI AISSA[17]
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Background: INTRODUCTION

We carried out a first national and multicentric study on the evaluation of the treatment with generic Imatinib (Imatib molecule used in Algeria) of patients followed for CML, involving 1007 patients recruited between 2007 and 2013, the results were presented to the North African congress of hematology in 2016 concluding to an overall survival (OS) at 84% at 08 years, significantly correlated with the sokal score (p <10-6). Event-free survival (EFS) at 08 years is 76%.

Aims: The objective of this study is to make an up-date, the follow-up of these patients and to assess OS, PFS and survival without events (EFS) at 12 years.

Methods: Material and methods

We evaluated the results of treatment with Imatib at 12 years in 881 patients, diagnosed between January 2007 and December 2013, with a median follow up of 72 months (60 to 144 months), The survival curves are established

according to the Kaplan method Meier, Descriptive analysis of quantitative variables by calculating means, medians. Descriptive analysis of qualitative variables in percentages and 95% confidence interval. The Chi2 test is used to compare between two variables.

Results:

At 12 years old Overall survival is 86%, the death rate between 8 and 12 years old is 9% of which only 03% are related to the disease which brings the overall survival rate to 88% if we only take into account of these. The PFS is 84%, with a rate of progression clearly falling from 05 years of evolution since, it is 11% at 05 years, 08% between 05 and 08 years, and is only 02 , 56% between 08 and 12 years old. The EFS is 66% at 5 years, 62% at 08 years and 60% at 12 years. The molecular remission rate for all is 64%, with 306 cases in MMR (34.7%), 119 cases in RM4 (13.5%), 81 cases in RM4, 5 (9.1%), 67 cases in RM5 (8.7%). 84 patients are not on MMR, and unfortunately almost a third of patients (27%) do not have monitoring due to lack of resources.

Conclusion:

In terms of long-term survival in CML, it is very difficult to do better than Imatinib. Generic Imatinib, an ITK which remains an excellent therapeutic option in terms of balance: efficacy and tolerance and cost. On the other hand, great efforts remain to be made in Algeria for better monitoring of patients in terms of molecular monitoring, and therapeutic reinforcement by the 2nd generation ITKs of patients at high potential risk.

CML AdvocatesNetwork

(PB1955) THE EVOLUTION OF THE TREATMENT OF CHRONIC MYELOID LEUKEMIA: A NATIONWIDE POPULATION-BASED STUDY IN TAIWAN

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Background:

Chronic myeloid leukemia (CML) is a hematologic neoplasm driven by unregulated tyrosine kinase signaling from acquiring the BCR-ABL fusion gene. The standardized incidence was 0.61 per 100,000 person-years in Taiwan in 2016. CML patients' outcomes have been remarkably improved with the advance of effective therapy with tyrosine kinase inhibitors (TKIs).

Aims:

We aim to investigate the evolution of CML treatment and patients' survival.

Methods:

We conducted a retrospective population-based study to assess the evolution of treatment and the improvement of outcomes in CML patients. All patients newly diagnosed with CML between January 1, 2000 and December 31, 2017 were recruited. The patients aged less than 20 years, did not receive TKI therapy were excluded. We evaluated the overall survival (OS) divided by three cohorts by the CML diagnosis year. We studied the three TKIs, imatinib, nilotinib, and dasatinib, which were reimbursed by our national insurance program. A multivariate Cox proportional hazards model was used to evaluate the effectiveness of the TKIs with adjustment of the risk factors for mortality in CML patients.

Results:

There were 2,401 CML patients in the final cohort, with a median age of 51 years (range 20–97). Of them, 60.1% were male. The most common comorbidities were hypertension (38.7%), diabetes mellitus (26.9%), and cerebrovascular accidents (25.7%). The 5-year OS for the cohorts years 2000–2004, 2005–2009, and 2010–2017 were 63.4%, 79.0%, 83.1%, respectively. In the univariate analysis, the CML patients treated with nilotinib and those treated with dasatinib had better OS in comparison with those

treated with imatinib (HR 0.48, 95% CI 0.31–0.73 and HR 0.52, 95% CI 0.35–0.76, respectively). However, the patients treated with three TKIs had similar OS in the multivariable analysis (adjusted HR 0.80, 95% CI 0.51–1.25 for nilotinib and adjusted HR 0.92, 95% CI 0.61–1.38 for dasatinib).

Summary/Conclusion:

The survival of CML patients has been dramatically improved in recent years. The patients treated with three TKIs as frontline treatment had similar OS after adjusting for potential confounders.

CML AdvocatesNetwork

(PB1956) PRELIMINARY RESULTS OF THE FIRST TKI DISCONTINUATION STUDY IN PATIENTS WITH CML WHO ACHIEVED DEEP AND SUSTAINED MOLECULAR REMISSION IN ARGENTINA (ARGENTINA STOP TRIAL - AST)

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Background:

Treatment discontinuation of tyrosine kinase inhibitors (TKI) in patients with chronic myeloid leukemia (CML) is safe. About half of patients in deep molecular response (DMR) sustain treatment-free remission (TFR) while those who don't regain molecular response after treatment reintroduction. In order to attempt TFR, intensive molecular monitoring (MM) by RT-qPCR in a standardized laboratory is mandatory. A robust predictor of prolonged TFR has not been reported yet.

Aims:

First, to guarantee adequate MM for TFR in Argentina; second, to characterize new prognostic biomarkers helpful to identify more accurately the patients who will be able to sustain the TFR.

Methods:

The AST contemplates the recruitment of patients with CML (typical *BCR-ABL1* transcripts b3a2 and/or b2a2) in chronic phase, treated with TKI who achieved DMR (≥$MR^{4.0}$), sustained for ≥ 2 years in a standardized laboratory and with ≥ 4 years of treatment. MM is carried out in 2 harmonized laboratories, monthly for the first 6 months, every 2 months until the year, and every 3 months during the second year. If patients lose $MR^{3.0}$ they restart

treatment immediately. In addition, at the time of discontinuation, at month 3, 12 and at any time when $MR^{3.0}$ is lost, the immunological profile of multiple subpopulations of Natural Killer cells (NK, $CD56^{+}CD3^{-}$) is analyzed by flow cytometry, with particular interest in subpopulation $CD57^{+}CD16^{+}CD158a/b^{+}$ defined as *tumor-induced memory like-NK* cells (TIML-NK).

Results:

To date we have analyzed 50 patients from 7 centers in Argentina (3 public and 4 private). Informed consent was obtained in all cases. Four patients failed screening; of the remaining 46, the median age is 58 years (24-85). Twenty-two patients (48%) were in low, fourteen (30%) in intermediate and ten (22%) in high Sokal risk score. Before discontinuation thirty-five patients took Imatinib (76%), and eleven took 2G-TKI (24%). Thirty-nine percent (18/46) of the patients achieved $MR^{3.0}$ before twelve months under TKI treatment. The median duration of treatment prior to discontinuation is 10.6 years (4.16-17.5). The average post-discontinuation follow-up time is 128 days (1-300). There are 6 patients (13%) who lost $MR^{3.0}$; one at month 2, three at month 3 and two at month 5, all of them immediately restarted the treatment. The remaining 40 still sustain MR without treatment (mean $\%BCR\text{-}ABL1^{IS}=0.008\%$). At the time of discontinuation, the median percentage of NK cells with respect to total lymphocytes is 14.7% (5–45%) for patients and 8.6% (3-14%) for healthy donors (n=8), suggesting a positive effect of the TKIs on that population. Patients show a two-group distribution for the presence of TIML-NK cells, a high (mean 63.3%) and a low (mean 34.1%) percentage populations are observed, with statistically significant difference ($p<0.01$). Interestingly, the mean value (60.9%) of TIML-NK cells of all patients (n=6) who lost $MR^{3.0}$ belongs to the high group.

Summary/Conclusion:

This is the first multicenter study of TKI discontinuation in real life in Argentina, which is currently in the enrollment phase of patients. Due to the short follow-up, results do not allow conclusions yet; however, the study of the immune system shows a phenotypic heterogeneity that may correlate with the clinical outcome of patients. This discontinuation study will allow significant saving of economic resources and may improve the quality of life of patients who currently suffer adverse effects of treatment.

CML AdvocatesNetwork

(PB1957) SECONDARY MALIGNANCIES IN CHRONIC MYELOID LEUKEMIA : A SINGLE CENTER EXPERIENCE

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Background:

Introduction of tyrosine kinase inhibitors (TKIs) in the treatment of chronic myeloid leukemia (CML) have dramatically changed the natural history of disease resulting in a high number of long term survivors. Novel attention is growing regarding therapy related complications, as development of secondary malignancies, that can negatively affect long term survival and quality of life of CML patients.

Aims:

Here we report data on secondary tumours diagnosed in CML patients treated with at least one type of TKIs, followed in our Institution and diagnosed since 01 September 1993 until 31 December 2018.

Methods:

We have collected retrospective data on secondary neoplasms occurring in 189 consecutive CML patients recorded in our database updated on 25 February 2020.

Results:

We have analyzed data regarding 189 patients with CML. One hundred fifteen were males (61%), 74 females (39%); median age at CML diagnosis was 56 years (range 59-88). Eleven patients (6%) experienced other cancer after a diagnosis of CML, 2 of them had consecutive 2 neoplasms so we documented a total of 13 second tumours. They were: 2 skin (15%) and 11 non cutaneous cancers (85%). The neoplasm were: 2 basal cell carcinoma, 2 prostatic , 2 lung, 1 metastatic breast, 1 colon, 1 pancreatic, 1 biliary tract, 1 thyroid, 1 renal cancers, 1 indolent mantle cell Non Hodgkin Lymphoma. Actually the breast and the thyroid cancers observed were relapse of previous cancers. Four patients died because of their solid tumours (2%).The median time between CML diagnosis and second malignancy diagnosis was 64 moths (range 36-142), the median age at second cancer was 55 years (range 47-73). Regarding the TKIs type: 6 patients were receiving imatinib at the moment of cancer occurrence (55%),1 dasatinib (9%), 4 nilotinib (36%). Four had received more then one line of therapy

(36%), and one of them underwent to hematopoietic stem cell transplantation before the TKIs era. In four cases TKI was stopped to avoid interference with chemotherapy treatment, but two patients resumed the drug because of hematological relapse.

Summary/Conclusion:

Although the role played in carcinogenicity by long exposition of TKI therapy and genetic instability in CML cells is not clear, we think that a special care in secondary cancers surveillance and early detection would be deserved to CML patients. Furthermore, studies are needed to better understand biological basis of carcinogenesis in people taking TKIs drugs and interaction between CML therapy and solid neoplasm treatments.

CML AdvocatesNetwork

(PB1958) IMPACT OF INEQUITIES IN ACCESS IN THE RESPONSES TO TYROSINE KINASE INHIBITORS IN COLOMBIAN PATIENTS WITH CHRONIC MYELOID LEUKEMIA: FIRST RENEHOC REPORT ON CML

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Background:

The introduction of tyrosine kinase inhibitors (TKI) changed the history of Chronic Myeloid Leukemia forever. However, multiple studies have shown that adherence to treatment is a key factor in achieving the best outcomes in terms of response depth and survival free of accelerated phase progression and blast crisis. Colombia has a mixed health system (public/private) that has delegated patient care and high-cost medication delivery to private actors poorly monitored and with different quality of care. There are two systems, the contributory (CS) and the subsidized (SS), which have highly unequal levels of access to treatments. The Colombian Association of Hematology and Oncology (ACHO), has been developing a registry of hematological diseases (RENEHOC), which, among other things, allow us to make visible the access problems that affect patients. This is the first report on CML.

Aims:

The aim of this firs report on CML is to compare outcomes in CML patients on different health care systems, and analyze other factors that affect progression free survival (PFS).

Methods:

An ambispective multicentric study was conducted based on data collected by RENEHOC during 2019. Medical records of CML patients in several centers in the most populated areas of Colombia, were reviewed. Descriptive statistics were used to analyze patient's demographic and clinical characteristics.Primary end point was Optimal Response (OR) defined as Complete Cytogenetic Response (CCyR), Mayor Molecuar Response (MMR) or 4.5MR at last visit. The Kaplan-Meier method was used to assess progression free survival (PFS) rates, defined as progression to accelerated/blastic phase or dead. Hazard Ratios (HR) using Cox proportional hazards regression modeling was estimated. Variables considered as prognostic factors for analysis were: Sex, age, phase and Sokal score at diagnosis, and type health care system (contributory and subsidized)

Results:

271 patients have been registered, mean age was 54 years (19-92), 60.1% (163) were males, most patient were diagnosed in chronic phase (91%) and around one third had low risk Sokal (27% low, 34% intermediate, 39% high). Imatinib was the first line treatment in two thirds of patients (170), followed by Dasatinib (56) and Nilotinib (45). 90% achieved CHR with first line treatment, 66% MMR and 53% 4.5 MR. 48% required a second line, most frequently used TKI in this setting was Dasatinib. At a median follow for the entire cohort of 61 months (1-204), 60% of patients were in OR, including 9 patients in treatment free remission (TFR). There were no significant differences between contributory and subsidiary cohorts in terms of patient or disease characteristics. 75% of patients were in OP at last visit in the CS in comparison to 51% for the SS's cohort. Only 7 patients died, all deads were CML related. Median PFS was not reached for CS vs 39 months for SS (p=0.058). The only significant prognosis factor associated with PFS was Sokal score at diagnosis. Mean PFS was 59 months for low Sokal and 45.2 for intermediate/high (p=0.0093) (Figure 1).

Summary/Conclusion:

The differences in access to medicines in relation to different insurance regimes, produce inequitable results in terms of lower optimal responses in the SS than in the CS. Other studies have shown the impact on PFS and OS

of the deeper responses. Analysis of the results in a larger cohort of patients is required to confirm these results. To our knowledge, this is the first time in the country that the impact of these attention inequalities in CML patient care have been demonstrated.

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(PB1959) LONG-TERM OUTCOMES OF TYROSINE KINASE INHIBITOR TREATMENT FOR CHRONIC MYELOID LEUKEMIA : A REAL WORLD DATA FROM MALAYSIA

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Background:

Tyrosine kinase inhibitors (TKI) are standard treatment of chronic myeloid leukemia (CML), and it has been used over the past 15 years in Malaysia. Most data of long term outcome from this treatment are from clinical trials.

Aims:

We conducted a study on major molecular remission (MMR) rate in chronic-phase CML patients based on real world data over the past 15 years.

Methods:

In this retrospective database analysis, we looked into all patients who received TKIs treatment at Ampang Hospital, a national hematology referral center in Malaysia since 2005. Primary objective is MMR rate in chronic-phase CML (have been treated with TKI for at least 18 months, or achieving MMR earlier than 18 month). Other long term analyses included MMR rate with different TKIs in chronic-phase CML patients, duration to reach MMR, and causes of failure to reach MMR. Imatinib was used as the first line TKI in most cases (93.1%). The mean follow-up duration was 72 months.

Results:

909 patients were treated with TKIs at Ampang Hospital since 2005. 179 patients excluded from this study are Ph-positive acute leukemia and patients with inadequate data. Out of 730 patients with CML, 601 was diagnosed with chronic-phase CML. The overall rate of MMR in CML was 54.38% (accelerated phase 32.4%, blast crisis 29.1%). The MMR rate for chronic-phase CML was 59.4% For TKIs in chronic-phase CML, Imatinib rate of achieving MMR was 47.3%. For Nilotinib, the MMR rate was 70.9%, and 70% of these patients were on Nilotinib as 2nd line TKI (after Imatinib). Patients on Nilotinib also achieved faster MMR compared to patients on Imatinib. We will further analyse causes of failure to reach MMR later.

Summary/Conclusion:

In our real world data, next generation TKI proved to achieve a rapid and higher rate of MMR among chronic-phase CML patients. This information is

important for a resource limited country like Malaysia to improve management of CML patients with expensive therapy. However, causes of failure to reach MMR must also be analysed to further optimize outcome of CML patients.

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(PB1960) THE IMPORTANCE OF MOLECULAR MONITORING CHRONIC MYELOID LEUKEMIA (CML) PATIENTS ON MONTHS 3 AND 12 IN LOW INCOME-COUNTRIES LIKE ALBANIA

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Background:

Chronic Myeloid Leukemia is a myeloproliferative neoplasm characterized by translocation of the genetic material between chromosomes 9 and 22 which form a fusion gene that is responsible for the abnormal tyrosine kinase activity. After the diagnosis has been confirmed monitoring of the patients using standardized techniques is very important to make treatment decisions on whether to increase the dosage or change to another type of tyrosine kinase inhibitor .

Aims: To better suit monitoring of Chronic Myeloid Leukemia patients to the income of each conutry and maybe trying to better use that income in providing another generation of TKI for our patients .

Methods:

We made a study in adult patients of Albanian ethnicity with Ph+ CML-CP within 6 months of diagnosis. Patients were randomized 1:1 to nilotinib 300 mg twice daily or imatinib 400 mg once daily. The patients were monitored for the response according to European Leukemia Net by reverse transcriptase quantitative PCR (RT-qPCR) at months 3,6,12 and 18.

Results:

Treatment with a tyrosine kinase inhibitor (TKI) targeting BCR-ABL1 is currently the standard of care for patients with chronic myeloid leukemia (CML) in chronic phase (CML-CP).

A total of 121 patients were randomized (nilotinib, n = 61; imatinib, n = 60) from May of 2011 to August 2014 at Hematology clinic ,University Hospital Center “Mother Teresa “. In this study, we present the results of a 48 months follow-up data of a study that was conducted to investigate nilotinib 300 mg twice daily vs imatinib 400 mg once daily in Albanian population.

We came to a very important result that on either arm of the study imatinib or nilotinib that patients who had an optimal response on month 3 had it on month 6 and patients who had an optimal response on month 12 had it on month 18 as well.

Summary/Conclusion:

In conclusion we suggest that maybe for low-income countries like Albania we should monitor our Chronic Myeloid Leukemia (CML) patients in chronic phase on months 3 and 12 instead of 3,6,12 and 18 because of the high cost of monitoring and of course not causing any harm to the patients after our results came out and maybe that money should go on trying to get more TKI than we actually have now which is only imatinib and nilotinib for the moment being .

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(PB1961) DEMOGRAPHIC/CLINICAL FEATURES AND TREATMENT OUTCOMES OF CHRONIC PHASE CHRONIC MYELOID LEUKEMIA PATIENTS IN TURKEY: REAL-WORLD DATA

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Background:

In treatment of patients with chronic myeloid leukemia (CML), there have been great advances in recent years and significant improvements have been achieved in survival rates with the introduction of tyrosine kinase inhibitors (TKIs). The choice of TKI is influenced by factors such as tolerability, adverse event profile, comorbidity, and concomitant drug use. Imatinib is the only reimbursed TKI for the first-line treatment in Turkey. Second generation TKIs are used in the next treatment steps.

Aims:

This study aimed to determine demographic and clinical features of chronic phase-CML patients in Turkey, to evaluate their treatment patterns and outcomes, and to detect overall survival (OS) rates.

Methods: In this national multicenter study, files of all patients diagnosed with

chronic phase-CML between January 2005 and January 2018 were retrospectively evaluated. Data on demographic and clinical information, treatments that patients received, and responses to treatments were collected from the records. Treatment responses were assessed according to the 2013 European LeukaemiaNet (ELN) recommendations for management of CML. OS rates and effective factors were investigated.

Results: This study included 861 CML patients (50.4% males) with the mean age of 51.9±15.6 years. The characteristics of the patients are summarized in Table 1. Of the patients, 49.4% were receiving a first-line treatment and 97.6% were using imatinib. There were switches among the first-line generic drugs in 32.9% of the patients and the most frequent reason of these switches was drug supply problem/copayments/drug access problem (48.2%). The rate of switch to the second-line treatment was 48.7% and the main reason was loss of drug efficacy (60%). Dasatinib was the most commonly used drug (57.3%) in the second-line treatment. The rate of switch to the third-line treatment was 25.7% and the most common reason was side effects (50.9%). The most common drug used in the third-line was nilotinib (59%). Of the patients, 2.9% were switched to the fourth-line treatment. The most common reason of this switch was loss of drug efficacy (75%). Ponatinib was the most frequently used drug (42.9%) in the fourth-line treatment. Fifty-five (6.4%) patients had died. The 1- and 10-year OS were 99.2% and 89.1%, respectively. OS was longer in females ($p=0.021$), in those without diabetes mellitus ($p=0.026$) and cardiovascular disease ($p<0.001$) at the diagnosis, and in those not receiving concomitant treatment ($p=0.007$) at the diagnosis. OS was also longer in those having hematological ($p<0.001$), molecular ($p<0.001$), and cytogenetic ($p<0.001$) responses. There was no significant impact of treatment switch on

Table 1. Demographic and clinical features of the chronic phase-CML patients

Features	N	Values
Age, year, median (Q1-Q3)	861	52 (40-64)
Age at diagnosis, year, median (Q1-Q3)	861	48 (36-60)
Sex, n (%)	861	
Female		427 (49.6)
Male		434 (50.4)
Presence of comorbidity at the diagnosis, n (%)		
None		572 (68.9)
1		157 (18.9)
2		67 (8.1)
3		27 (3.3)
4		7 (0.8)
Comorbidities at the diagnosis, n (%)		
Diabetes mellitus	823	87 (10.5)
Cardiovascular disease	841	117 (13.9)
Pulmonary disease	840	28 (3.3)
Other	841	171 (20.3)
Concomitant treatment at the diagnosis, n (%)	664	148 (22.3)
Current CML treatment, n (%)	861	
First-line		425 (49.4)
Second-line		178 (20.7)
Third-line		52 (6.0)
Fourth-line		5 (0.6)
Other*		201 (23.3)
Hematological response, n (%)	663	633 (95.5)
Duration of hematological response, month, median (Q1-Q3)	591	2.3 (1.1-3)
Molecular response, n (%)	649	507 (78.1)
Duration of molecular response, month, median (Q1-Q3)	351	12 (7.5-17)
Cytogenetic response, n (%)	468	354 (75.6)
Duration of cytogenetic response, month, median (Q1-Q3)	317	12 (7.2-21.4)

* Patients who were lost in follow-up or had missing data
Q1, 25th percentile; Q3, 75th percentile

OS.

Summary/Conclusion:

This study examined demographic/clinical characteristics, treatment patterns, and outcomes on of the largest cohorts of CML patients in Turkey. The patient population was relatively young, but had a significant rate of comorbidities. Response rates to TKI treatment were satisfactory. Comorbidities had significant impact on OS. In treatment choice, in addition to tolerability and side effects, presence of comorbidities should also be taken into account and treatment should be personalized.

CML AdvocatesNetwork

(PB1962) AN INVESTIGATION SURVEY IN CENTRAL CHINA: TKI DE-ESCALATION TREAMENT IN CHRONIC MYELOID LEUKEMIA PATIENTS

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Background:

Previously study has been reported long-term tyrosine kinase inhibitors (TKI) treatment leads to 86% major molecular response (MMR) and 92% progression-free survival (PFS), but is costly and associated with significant side effects. Stopping treatment is therefore of considerable interest to both patients and their physicians, but data from multiple treatment cessation studies indicate that relapse rates of 45-64%. Treatment de-escalation as a prelude to complete cessation has been reported as a strategy improves the fraction of patients with treatment free remission (The DESTINY trial), which has not been well investigated in Chinese clinical setting.

Aims:

Describe and assess whether CML patients with deep-level remission can maintain a long-term MMR status after using de-escalation treatment of TKIs.

Methods:

We conducted a multicenter phase II trial to test the safety and efficacy of half standard TKI dose after at least 1 years of MR4.0-equivalent (chiCTR1800014938). Molecular recurrence was defined as loss of MMR (BCR-ABL1:ABL1 ratio >0·1%).

Results:

Patients were enrolled at 4 participating institutions from May 2015 to December 2019. 18 patients are included, 61.1% males. Median age was 48 years. TKI therapy duration 97.5(67-136) months and preceding MR4.0 or MR4.0 equivalent period 37.5(12-98) months. De-escalation treatment duration 12(1-32) months. 10 of 18 patients have completed de-escalation phase for 12 months. One of the patient after a reduction of 32 months, the drug was sequentially discontinued, and the MR4 was continuously maintained for 18 months. 5 of 10 patients who were not sequentially get

cessation maintaining the stable RFS over 14 (12-18) months. But 3 of 10, whom were sequentially get cessation, loss of MMR in 2 to 6 months; one of them regained MMR in 4 months on half-dose TKI resumption; the other two still under observation by half-dose TKI resumption. Individual side-effects (lethargy, diarrhea, rash, nausea, periorbital edema, and hair thinning) all improved during de-escalation.

Summary/Conclusion:

TKI de-escalation is safe for most patients with excellent responses to TKI therapy, and is associated with improvement in side-effects. The effection of the strategy by treatment de-escalation as a prelude to complete cessation need to further investigation in larger prospective trials.

CML AdvocatesNetwork

(PB1963) BCR-ABL1 TRANSCRIPTS E13A2 AND E14A2 IN RELATION TO SURVIVAL AND MOLECULAR RESPONSES IN CML PATIENTS IN BOSNIA

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Background:

Chronic myeloid leukaemia (CML) is a clonal disease of the haematopoietic stem cells that is driven by the chimeric BCR-ABL1 protein with aberrant tyrosine kinase activity. Chimeric BCR-ABL1 p210 protein results from several types of transcripts, where e13a2 and e14a2 account for the vast majority of cases.

Aims:

We analysed the correlation between *BCR-ABL1* transcript type and overall survival, the probability of achieving CCyR (complete cytogenetic response), MMR (major molecular response), and deep molecular response (MR4 and MR5).

Methods:

Out of 245 newly diagnosed CML patients in chronic phase who started TKI therapy in the period from August 2005 to December 2019, 69 patients had available clinical data and transcript type. Transcript type was determined with reverse transcription PCR (RT-PCR) using peripheral blood at diagnosis, as described previously (Branford and Hughes, 2006). Patients were categorised based on the transcript type into e13a2, e14a2, and atypical. Standard patients' variables were collected including TKI treatment (imatinib and/or nilotinib), OS, CCyR, MMR, MR4 and MR5. Survival probabilities were estimated using the Kaplan-Meier method and compared using the log-rank test.

Results:

We analysed 69 patients with median follow-up of 74 months. Three patients died (one patient had e13a2, one had e14a2 and one had both). Regarding transcript type, 29 patients (42%) had e13a2, 38 patients (55%) had e14a2, 1 patient (1.5%) had both transcripts, and 1 patient (1.5%) e1a2/e14a2. Patients with e13a2 transcript were on imatinib (37%), nilotinib (48%), and 15% of

patients switched from imatinib to nilotinib. Patients with e14a2 were on imatinib (50%), nilotinib (31%), and 19% of patients switched. The patient with both transcripts switched from imatinib to nilotinib. The patient with atypical transcript e1a2/e14a2 was treated with first-line nilotinib. At 100 months, overall survival was not significantly different between e13a2 *vs.* 14a2 group (100% *vs.* 95%, p=0.54). Regarding CCyR at 60 months, there was no significant difference between transcript types (100% in e13a2 group *vs.* 85% in e14a2 group, p=0.11). Regarding MMR at 60 months, there was no significant difference between transcript types (91% in e13a2 group *vs*. 84% in e14a2 group, p=0.61). No significant difference was found in achievement of MR4 or MR5 in analysed patients.

Summary/Conclusion:

Our study showed that *BCR-ABL1* transcript type was not associated with differences in overall survival, the achievement of CCyR, MMR, nor deep molecular responses in CML patients in Bosnia.

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(PB1963) BCR-ABL1 TRANSCRIPTS E13A2 AND E14A2 IN RELATION TO SURVIVAL AND MOLECULAR RESPONSES IN CML PATIENTS IN BOSNIA

Amina Kurtovic-Kozaric*[1], Erna Islamagic[2], Semir Mesanovic[3], Adnan Burekovic[4], Amna Uzunovic[4], Sabira Kurtovic[5]
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Background:

Chronic myeloid leukaemia (CML) is a clonal disease of the haematopoietic stem cells that is driven by the chimeric BCR-ABL1 protein with aberrant tyrosine kinase activity. Chimeric BCR-ABL1 p210 protein results from several types of transcripts, where e13a2 and e14a2 account for the vast majority of cases.

Aims:

We analysed the correlation between *BCR-ABL1* transcript type and overall survival, the probability of achieving CCyR (complete cytogenetic response), MMR (major molecular response), and deep molecular response (MR4 and MR5).

Methods:

Out of 245 newly diagnosed CML patients in chronic phase who started TKI therapy in the period from August 2005 to December 2019, 69 patients had available clinical data and transcript type. Transcript type was determined with reverse transcription PCR (RT-PCR) using peripheral blood at diagnosis, as described previously (Branford and Hughes, 2006). Patients were categorised based on the transcript type into e13a2, e14a2, and atypical. Standard patients' variables were collected including TKI treatment (imatinib and/or nilotinib), OS, CCyR, MMR, MR4 and MR5. Survival probabilities were estimated using the Kaplan-Meier method and compared using the log-rank test.

Results:

We analysed 69 patients with median follow-up of 74 months. Three patients died (one patient had e13a2, one had e14a2 and one had both). Regarding transcript type, 29 patients (42%) had e13a2, 38 patients (55%) had e14a2, 1 patient (1.5%) had both transcripts, and 1 patient (1.5%) e1a2/e14a2. Patients with e13a2 transcript were on imatinib (37%), nilotinib (48%), and 15% of

patients switched from imatinib to nilotinib. Patients with e14a2 were on imatinib (50%), nilotinib (31%), and 19% of patients switched. The patient with both transcripts switched from imatinib to nilotinib. The patient with atypical transcript e1a2/e14a2 was treated with first-line nilotinib. At 100 months, overall survival was not significantly different between e13a2 *vs.* 14a2 group (100% *vs.* 95%, p=0.54). Regarding CCyR at 60 months, there was no significant difference between transcript types (100% in e13a2 group *vs.* 85% in e14a2 group, p=0.11). Regarding MMR at 60 months, there was no significant difference between transcript types (91% in e13a2 group *vs*. 84% in e14a2 group, p=0.61). No significant difference was found in achievement of MR4 or MR5 in analysed patients.

Summary/Conclusion:

Our study showed that *BCR-ABL1* transcript type was not associated with differences in overall survival, the achievement of CCyR, MMR, nor deep molecular responses in CML patients in Bosnia.

(PB1964) CHRONIC MYELOID LEUKEMIA: ABOUT 114 CASES

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Background:

Chronic myeloid leukemia (CML) is a rare myeloproliferative neoplasia whose tumor that results in a molecular marker which is the BCR-ABL fusion gene, which induces the production of chimeric protein which, by its deregulated tyrosine kinase activity, is responsible for the disease.

Aims:

The aim is to report the experience of the clinical hematology and internal medicine department of the Ibn-Sina University Hospital in Rabat in the management of CML

Methods:

We conducted a retrospective study, of descriptive and analytical type, monocentric, on patients treated in our service for CML, over a period of 12 years, spread out from January 2005 to December 2017.

Results:

We collected 114 patients, including 66 women and 48 men. The average age of the patients is 46.52 years (± 29.52) [17 - 76 years]. Clinically 23% of the patients had an infectious syndrome, 11% had an hemorrhagic syndrome, and 78.4% had a palpable splenomegaly. Biologically, 91% of patients had anemia, myelemia was found in 89% of patients. At diagnosis, 75.4% of patients were in the chronic phase, 10.5% accelerated and 2.6% accutated. The Philadelphia chromosome was detected in 92% of cases, additional cytogenetic abnormalities were found in 11.9% of cases. The search for the Bcr / Abl transcript was carried out in 55.3% of the patients. Vitamin B12 was measured in 24 patients, it decreased in 4 of them, and elevated in 13 patients. Prognostic scores could be calculated in 71.1% of patients. The SOKAL score was intermediate in 35.1% of cases and high in 32.5% of cases. 20 patients had complications in the diagnosis of the disease: 7 patients had a significant hemorrhagic syndrome, 4 had a thrombotic event including 1 pulmonary embolism and 1 ischemic stroke, 8 patients were complicated by severe sepsis including one case of pulmonary tuberculosis. Therapeutically, 30.3% of patients were treated with Hydroxyurea alone, 36% were threated buy Imatinib, the combination of the 2 treatments was noted in 30.3% of patients.

36% of patients had side effects to ITK, 78% of which were haematological. Adherence to treatment was good in 61% of patients. The cytogenetic response was obtained in 58.4% of the patients evaluated. The molecular response was major in 71% of the patients. 7 patients were switched to a 2nd generation ITK type Nilotinib and 1 patient to Dasatinib. The evolution was marked by the acceleration of the disease in 12 patients, and by the accusation in 11 patients. 7 deaths were noted in our series. In addition, 1 patient presented with a subarachnoid infiltration for which she benefited from therapeutic intra-thecals based on: aracytine, corticoids and methotrexate. 1 patient had a cerebellar location, and 1 patient had ocular involvement. Pregnancy was noted in one patient, treated with pegylated interferon with haematological remission and delivery without incident.

Summary/Conclusion:

Tyrosine kinase inhibitors have revolutionized the management of this malignant hemopathy, and have transformed its course and prognosis.

CML AdvocatesNetwork

(PB1965) RARE BCR-ABL TRANSCRIPTS IN CML: E6A2 WITH EXTRAMEDULLARY LESIONS AND UNUSUAL E2A2 WITH PATIAL DELETION AND STIMULTANEOUS INSERTION (CASE REPORTS)

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Background:

Philadelphia chromosome (Ph) results from the reciprocal translocation t(9;22) and is a hallmark for chronic myelogenous leukemia (CML). Ph gives rise to the fusion BCR-ABL ocogene and oncoprotein with enhanced tyrosine kinase activity. BCR-ABL mRNA transcripts are usually tested in order to confirm CML diagnosis and to monitor minimal residual disease (MRD). Rare variants of BCR-ABL may be underreported as a result of failure of some PCR primer sets to anneal to BCR and ABL sequences around of unusual breakpoints. False negative PCR results may hinder or delay CML diagnosis and result in misleading MRD assessment. Clinical peculiarities of CML with rare BCR-ABL transcripts still need to be thoroughly described.

Aims:

To report two novel cases of CML pts with rare BCR-ABL mRNA transcripts.

Methods:

Total RNA was extracted from peripheral blood (PB) and bone marrow (BM) samples of CML pts. cDNA was developed with random hexamer primers. Both quantitative RQ PCR and qualitative conventional PCR were performed. Products of conventional PCR were detected and purified by means of polyacrylamide gel electrophoresis. PCR products were directly sequenced and analysed.

Results:

We report here two cases of CML pts with unusual BCR-ABL mRNA transcripts. First pt was 60 yo male with CML manifested in the March 2016 when he had suffered from a pain in the left hypochondrium as a result of splenomegaly (130x60x160 mm). At that moment in BM there were 48% blasts and 7% myelocytes. Standard kariotype analysis revealed 80% of Ph-positive cells.

Local lab failed to find BCR-ABL mRNA expression. This pt had been receiving 400 mg/d of imatinib for 3 years. In the May 2019 MRT investigation found out a soft tissue tumor bulk (57x26x50 mm) within the body of L1 vertebra as well as multiple tumor loci within the chest, lower back vertebrae and pelvic bones. FISH analisys showed 1% of Ph in BM, tumor biopsy was Ph-positive. In our lab PB and BM samples were tested and we have found expression of a rare type of the e6a2 BCR-ABL mRNA (Fig.1). Due to imatinib resistance the treatment was modified for 400-600 mg/d of nilotinib. It helped to reduce the size of the tumor in the L1 vertebra to 12x18x32 mm. The other pt was 32 yo female in whom we found out previously unreported variant of the b2a2 BCR-ABL mRNA transcript. The 48 bp of the 3'-part of the b2 BCR exon in BCR-ABL transcript was deleted and reading frame was broken. However, the reading frame had been restored by insertion of 12 bp GGAGAGGCCTAA that were originated from 1b intron (Fig.2). Common RQ PCR primer set was not able to amplify this new variant of BCR-ABL transcript and showed false negative result. Successful RQ PCR for this pt was performed by replacing direct b2 BCR exon primer for another one which anneals within b1 BCR exon. BM cells of this pt had complicated kariotype of 46,XX,t(2;3;7;10)(q13;q21;p15;q22),t(7;13)(q36;q13),t(9;22)(q34;q11)[20].

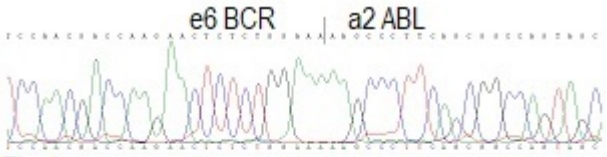

Fig.1

Fig.2

Summary/Conclusion:

Two new cases of CML pts with rare BCR-ABL transcripts were described. It is for the first time that in CMP pt with e6a2 BCR-ABL transcript intra L1 vertebra extramedullary imatinib resustant Ph-positive tumor was found. Novel b2a2 BCR-ABL transcript variant was discovered with 48 bp deletion/12 bp insertion of b2 exon. Our data suggest that structural variants of BCR-ABL transcripts may greatly influence CML clinical course and also hinder and complicate establishment of correct diagnosis.

CML AdvocatesNetwork

(PB1966) EVALUATION OF THE SELECTIVITY OF BCR-ABL TYROSINE KINASE INHIBITORS (TKIS): A SYSTEMATIC REVIEW

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Background:

Although chronic myeloid leukemia is now a treatable chronic disease, patients need to take BCR-ABL tyrosine kinase inhibitors (TKIs) over long periods. Regrettably, there is growing evidence of cardiovascular adverse events associated with new-generation BCR-ABK TKIs. Due to the lack of specificity for BCR-ABL, especially for new-generation TKIs, acquiring selectivity profiles is from the utmost importance.

Aims:

This systematic review aims to summarize all available data from the literature related to the selectivity of BCR-ABL TKIs to emit hypotheses about inhibited tyrosine kinases that might be involved in cardiovascular events.

Methods:

Two independent reviewers screened titles and abstracts according to a predefined search strategy through Pubmed, Scopus and Cochrane Library. Included articles are those describing at least one TKI off-target for at least one of the five BCR-ABL TKI. Extraction of the results of the included studies have been performed by the two reviewers independently in a standardized extraction form.

Results:

The screening of 2,850 articles led to the identification of 27 studies that assessed at least one BCR-ABL TKI off-target. Through these 27 studies, 465 kinases have been tested. Each BCR-ABL TKI has a specific inhibitory profile. Imatinib is the most selective and the most studied. This review pointed out discrepancy on 210 tyrosine kinases and considerable diversity in methods used to study TKI specificity.

This review identifies tyrosine kinases potentially implicated in the cardiovascular diseases that occurred during new-generations TKIs treatment. Among the tyrosine kinases inhibited by the new-generation TKIs but not by imatinib, the ephrin family and the tyrosine kinase HCK are implicated in atherosclerosis: EphA2 promotes endothelial cell inflammatory response whereas HCK is implicated in atherosclerosis plaque formation.

Summary/Conclusion:

The review points out discrepancy in inhibitory profiles of BCR-ABL TKIs from 27 experimental studies and considerable diversity in methods used to study TKI specificity.

CML AdvocatesNetwork

(PB1967) REAL WORLD DATA OF TREATMENT FREE REMISSION IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA (CML) TREATED AT TERTIARY CARE ONCOLOGY CENTRE FROM INDIA

Lakhan Kashyap*[1], Suresh Kumar[1], Yashwant Kashyap[1], Tanmoy Mandal[1], Ravindra Nandhana[1], Avinash Bonda[1], Lingraj Nayak[1], Nikhil Patkar[2], Bhausaheb Bagal[1], Hari Menon[3], Reena Nair[4]
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Background:

ABL1 tyrosine kinase inhibitors (TKI) have dramatically improved outcome in CML patients with overall survival of the patients reaching close to healthy population. Apart from cost, prolonged treatment with TKI is associated with adverse effects which may affect quality of life of the patients and adherence to treatment. Clinical trials have shown that treatment with TKI can be safely discontinued in 50% of CML patients, however this require careful case selection and stringent monitoring. There is dearth of data for TFR outside clinical trials especially for Indian population. We did retrospective analysis of our institutional data to assess feasibility of TFR in Indian population.

Aims:

To report real world outcome of treatment free remission (TFR) in CML patients.

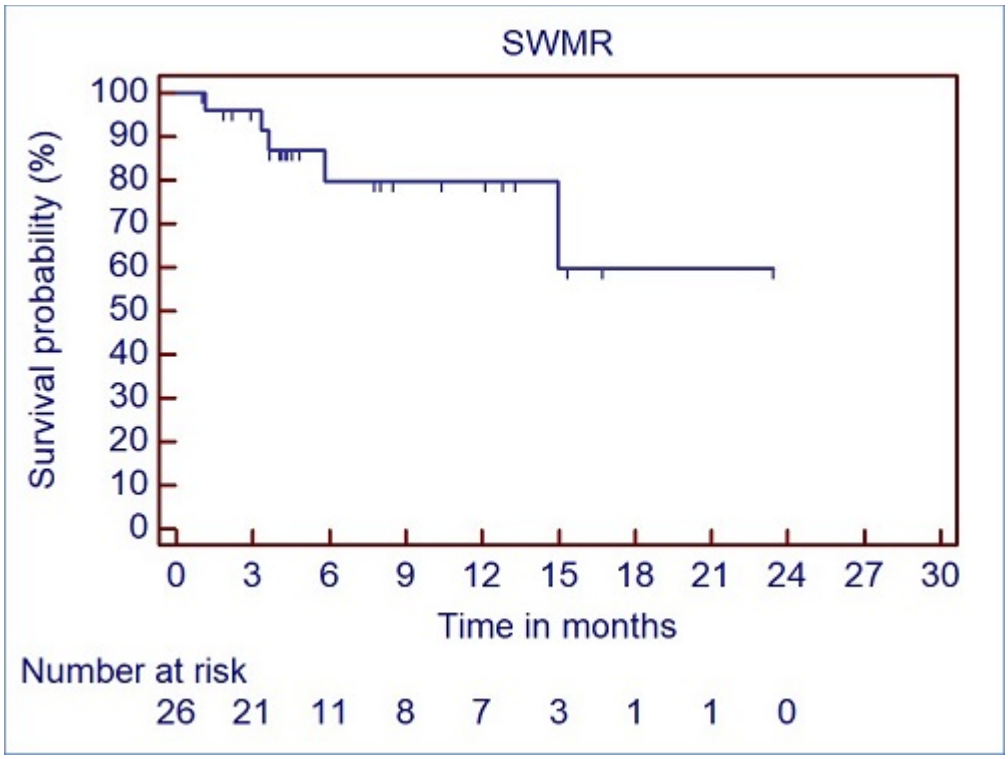
Methods:

We retrospectively reviewed data of CML patients treated at our institute from 1995 to 2013. We identified 26 patients who stopped TKI due to intolerance or after discussion about TFR. We analysed the data for molecular relapse (loss of major molecular response, MMR), survival without molecular relapse (SWMR) and factors affecting SWMR. SPSS 24 was used for statistical analysis and p value of 0.05 was taken as statistically significant.

Results:

Out of 26 patients, five patients discontinued TKI due to intolerance (progressive renal dysfunction in two, recurrent subconjunctival haemorrhage in one, pulmonary arterial hypertension in one and sustained myalgia in one patient) and in rest of the patients TKI was discontinued after mutual discussion between patient and clinician. Median age at TKI discontinuation was 59 years (42 – 81 years) and 88% of patients were male. Four and fifteen patients had EUTOS low and high risk CML respectively at the time of diagnosis while data

was missing for seven patients. Twenty-five patients received imatinib and one patient received dasatinib prior to discontinuation of TKI. Median duration of TKI therapy prior to TFR was 132 months (34 – 206 months). Deep molecular remission (DMR) i.e MR4 was attained in 25 patients while best molecular response in remaining one patient was MMR. Median duration of DMR was 36 months (2-76 months) and stable DMR (DMR for ≥ 2 years) was attained in 72% of patients. At median follow-up of 8 months, five patients (19%) had molecular relapse of CML. All five patients had molecular relapse within 6 months of TKI discontinuation with median time to loss of MMR being 3.6 months (1-14 months). Median SWMR was not reached while SWMR at 3 months and 6 months was 95% and 80% respectively. In comparison to patients in TFR, patients with molecular relapse were younger (53 vs 61 years), had higher proportion of EUTOS high risk CML (40% vs 10%), had lower proportion of SDMR (60% vs 67%), received TKI for shorter duration (79 vs 142 months) and had shorter duration of deep molecular remission after TKI discontinuation (1 vs 4 months). However, none of these factors were found statistically significant in multivariate analysis using cox proportional hazard model. After TKI discontinuation, 10 patients (38%) developed mild to moderate musculo-skeletal adverse events.



Summary/Conclusion:

TFR is feasible and safe in clinical practice with comparable outcomes to that reported in clinical trials.

CML AdvocatesNetwork

(PB1968) A CASE OF PRELEUKEMIC CHRONIC MYELOID LEUKEMIA FOLLOWING CHEMOTHERAPY AND AUTOLOGOUS TRANSPLANTATION FOR T-LYMPHOBLASTIC LYMPHOMA

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Background:

The Philadelphia chromosome, which harbors the BCR-ABL1, could be induced after cytotoxic therapy. In therapy related CML, most patient present clinical features of CML like leukocytosis or anemia. Meanwhile, there have been a few cases where BCR-ABL1 have been detected, even though the patients did not exhibit clinical features of CML (preleukemic CML). However, most cases of preleukemic CML have not been associated with cytotoxic therapy.

Aims:

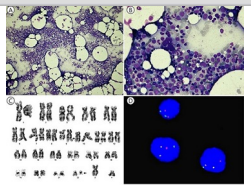
Herein, we report a rare case of BCR-ABL1-positive bone marrow in a patient with recurrent lymphoma 31 months after treatment for T-lymphoblastic lymphoma (T-LBL), who did not exhibit the clinical features of CML.

Methods:

A 37-year-old man presenting with a mass in the left oropharynx in November 2016, and was diagnosed with T-LBL. His bone marrow presented 46,XY [20], with no evidence of lymphoma. He received left tonsillectomy and four cycles of systemic chemotherapy. He achieved complete remission in December 2016 and subsequently underwent autologous stem cell transplantation in May 2017. Lymphoma relapsed in his right tonsil in July 2019. Complete blood count (CBC) results were not remarkable. Bone marrow examination showed no evidence of CML or lymphoma (Fig. 1A and 1B). However, 46,XY,t(9;22)(q34;q11.2)[15]/46,XY[5] karyotype was detected (Fig. 1C). Additionally, FISH studies and real-time PCR analysis were conducted.

Results:

FISH studies revealed the fusion of the ABL1 and BCR genes in 76.5% of metaphases (Fig. 1D). Real time PCR revealed a normalized copy number of 29.51 for minor BCR-ABL1 (e1a2). The patient was diagnosed with recurrent T-LBL and preleukemic CML. He was treated for relapsed lymphoma; regular examination for preleukemic CML was scheduled without tyrosine kinase

inhibitor therapy. 

Summary/Conclusion:

In previsous preleukemic tr-CML cases, the presence of the BCR-ABL1 fusion gene before initial therapy was not evaluated. Contrarily, in this study, chemotherapy-induced preleukemic CML was supported by the presence of normal chromosomes in the patient's bone marrow karyotype before chemotherapy. We believe that this is the first reported case of preleukemic CML that occurred post cytotoxic therapy for T-LBL.

CML AdvocatesNetwork

(PB1969) #10YEARCHALLENGE CHRONIC MYELOID LEUKEMIA: SINGLE CENTER REAL-LIFE EXPERIENCE ON CML MANAGEMENT. OUTCOMES OF EVOLVING TREATMENT STRATEGIES.

Gianni Binotto*[1], Luca Frison[1], Fabio D'Amore[1], Roberta Bertorelle[2], Laura Bonaldi[2], Ilaria Gianesello[1], Fabrizio Vianello[1], Gianpietro Semenzato[1]
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Background:

Chronic myeloid leukemia (CML) management has undergone continuous evolution over the past 10 years. Thanks to the availability of second and third generation tyrosine kinase inhibitors (TKIs), different therapeutic strategies, tailored to patient and disease characteristics, have been applied. As a result, CML patients nowadays can benefit from a survival more closely resembling to that of general population, the chance to discontinue treatment (under certain conditions), an improved tolerability of treatment through TKI dose optimization.

Aims:

We sought to evaluate the impact of different CML treatment strategies on patients' outcome, according to the period of diagnosis, in a "real life" single center cohort.

Methods: A total of 82 CML patients included in the analysis were divided in two cohorts based on the period of diagnosis (interval 1: 2010-2014, 40 pts; interval 2: 2015-2019, 42 pts). Responses were stated according to ELN2013 recommendations. Failure free survival (FFS) was calculated from the beginning of TKI therapy to the date of any of the following events: progression to FA/CB, death from any cause at any time, interruption of the treatment for primary or secondary resistance or intolerance. Overall survival (OS) was measured from the start of TKI to the date of death for any cause at any time. Baseline patient characteristics were compared between groups using the Pearson chi-square or the Fisher's exact test for categorical variables and the U Mann-Whitney test for continuous variables. FFS and OS were calculated using the Kaplan-Meier method and the values were compared using the long-rank test.

Results: No significant differences between the two groups regarding age, gender, Sokal/ELTS risk stratification were observed (table 1). The median follow-up was 82 months for the first and 21 months for the second cohort (P=0.001). Higher percentage of patients were treated with imatinib frontline (85%) in the first half of the decade (independently from risk stratification) compared to 59.5% in the 2015-19 interval period, where Sokal score

influenced the TKI selection (imatinib use in high risk 40% vs 57.5% in non-high risk patients). The proportion of early molecular responses was not found significantly different in the two periods (72.5% vs 73.7%, P=0.55), as well as the rate of major (MR3) and deep (DMR) molecular responses (90% vs 84.8%, P=0.37). The extended use of 2GTKIs in the second five years allowed a faster achievement of MR3 (median time: 9.2 vs 11.7 months) and DMR (11.8 vs 20.3 months). Interestingly, despite a significant difference in failure-free survival between frontline imatinib vs 2GTKIs, (50.8% vs 17.4%, P = 0.006), a substantial overlap in the medium and long term efficacy between sequential strategy (Imatinib plus 2GTKI) vs frontline use of 2GTKIs was observed. The majority of patients of the entire cohort (67%) are currently receiving reduced doses of TKI. Most of them at the last follow-up has at least major molecular response (73.7%) with a relatively low rate of severe adverse events and progressions documented; 62.1% are on treatment 2GTKIs.

Table 1. *Baseline patients characteristics.*

	GLOBAL	2010-14	2015-19	
Sex	%	%	%	P=0.192
M	53.7	47.5	59.5	
F	46.3	52.5	40.5	
Mean age at diagnosis (years)	60.9 (21.8 – 87.2)	58.8	59.9	
Transcript				P=0.10
b2a2	42.7	50	35.7	
b3a2	36.6	25	47.6	
b3a2/b2a2	18.3	25	11.9	
Others (p190, p230)	2.4	-	4.8	
SOKAL				P=0.26
Low	32.9	42.5	23.8	
Intermediate	54.9	47.5	61.9	
High	11	10	11.9	
Not evaluable	1.2	0	2.4	
ELTS				P=0.79
Low	46.3	47.5	45.2	
Intermediate	36.6	37.5	35.7	
High	15.9	15	16.7	
Not evaluable	1.2	0	2.4	

Summary/Conclusion:

The use of imatinib in frontline setting still represents an option able to offer a favorable outcome, especially in a sequential treatment strategy. The increase in the use of 2GTKIs in 1st line in the period 2015-19 has led to a reduction of failures and faster achievement of optimal responses. Treatment optimization to the minimum effective dose is a feasible approach in optimal responders, ensuring the maintenance of an adequate response in the face of less toxicity.

CML AdvocatesNetwork

(PB1970) THERAPEUTIC RESULTS OF SECOND GENERATION TKI IN THE TREATMENT OF CHRONIC MYELOID LEUKEMIA

Yousra Fakhfakh[1], Olfa Kassar*[1], Latifa Khalifa[1], Ines Turki[1], Fatma Ben Said[1], Semia Mnif[2], Rim Frikha[3], Hatem Belaaj[1], Maha Charfi[1], Manel Ghorbel[1], Imen Frikha[1], Imen Ben amor[1], Moez Mdhaffar[1], Sondes Hdiji[1], Moez Elloumi[1]
[1]hematology, university of Sfax, Sfax, Tunisia, [2]hematobiology, university of Sousse, Sousse, Tunisia, [3]hematobiology, university of Sfax, Sfax, Tunisia

Background:

The introduction of Tyrosine Kinase Inhibitor (TKI) therapy targeted at bcr-abl kinase dramatically changed the treatment and natural history of chronic myeloid leukemia (CML). However, approximately 21–37% of CML patients do not benefit from the first generation TKI imatinib due to intolerance or development of resistance.

Aims:

We report our experience with TKI second generation in the treatment of CML in southern Tunisia.

Methods:

Our study is retrospective. We included patients with CML in chronic or accelerated phase treated with second generation (2G) TKI over the period January 2011-December 2018. Patients received either oral dasatinib (100 mg once daily if chronic phase and 140 mg if accelerated phase) or oral Nilotinib (400 mg X 2/day). Through the analysis of the hematological response, the cytogenetic response and the molecular response, we classified the cases according to the criteria of ELN 2013 in optimal response, suboptimal and failure.

Results:

We collected 61 cases of CML treated with 2G TKI: 21 Dasatinib (34%) and 40 Nilotinb (66%). The sex ratio was 1.1 and the median age was 45 years (19-77 years). Sixty one patients were in the chronic phase (94%) and 2 in the accelerated phase (6%). According to the Sokal score, patients were classified as low, intermediate and high risk in 28%, 40% and 32% of cases, respectively. Fifty five patients (87%) had switched from Imatinib because of the development of resistance, 8 (13%) had switched because of Imatinib intolerance. The cumulative 6 and 12 month complete cytogenetic response were respectively 70% and 83% of cases. The 12 month major molecular response was 76%. According to the ELN criteria 2013, an optimal response, suboptimal and failure at 6 months were respectively 81%, 3% and 16% out of evaluable cases. A hematologic toxicity of TKI SG has been noted in 32% of

patients. 5 years overall survival and events free survival were 88% and 69% respectively.

Summary/Conclusion:

The use of 2G TKI has salvaged the two third of Imatinib resistant patients in our series. Our preliminary results are encouraging and similar to those reported to the literature with an acceptable safety profile. Better management of the use of 2G TKI may improve our CML results therapy (early TKI switch and even 2G TKI in first line therapy).

CML AdvocatesNetwork

(PB1971) PONS - A PHASE 2 STUDY WITH PONATINIB AS A 2ND LINE THERAPY FOR PATIENTS WITH CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE WHO ARE RESISTANT OR INTOLERANT TO PRIOR 1ST LINE TKI

Philipp Le Coutre*[1], Haifa Kathrin Al-Ali[2], Martina Crysandt[3], Ahmet Elmaagacli[4], Joachim Göthert[5], Martin Griesshammer[6], Carsten Hirt[7], Andreas Hochhaus[8], Johanna Homfeld[9], Susanne Saußele[10], Christian Schmidt[7], Frank Stegelmann[11], Andreas Burchert[12]
[1]Charité, Berlin, Germany, [2]Devision of Hematology, University of Halle, Halle, Germany, [3]Department of Hematology, Medical Faculty Aachen, Aachen, Germany, [4]Devision of Hematology, Asklepios Klinik St. Georg, Hamburg, Germany, [5]Department of Hematology, University Hospital Essen, Essen, Germany, [6]University Clinic for Hematology, Oncology, Hemostaseology, and Palliative Care, Johannes Wesling Medical Center Minden, UKRUB, University of Bochum, Moinden, Germany, [7]Department of Internal Medicine C, Hematology and Oncology, Greifswald University Medical Center, Greifswald, Germany, [8]Department of Hematology/Oncology, Clinic of Internal Medicine II, Jena University Hospital, Jena, Germany, [9]GWT-TUD GmbH, Dresden, Germany, [10]Department of Hematology and Oncology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany, [11]Department of Internal Medicine III, University Hospital Ulm, Ulm, Germany, [12]Department of Internal Medicine, Hematology, Oncology and Immunology, University Hospital Marburg, Marburg, Germany

Background:

Ponatinib, an approved oral tyrosine kinase inhibitor (TKI), has potent activity against native BCR-ABL1 and resistant mutants, including the T315I mutant. While continuing analysis of the phase 2 PACE trial have shown higher incidence of arterial occlusive events (AOEs) with a longer follow up, the exposure-adjusted incidence did not increase over time in the PACE patient population. Additionally, patients with CP-CML who had fewer prior TKIs appeared to exhibit better efficacy and safety profiles.

Aims:

This non-randomized, single arm phase 2 trial explores the activity and safety of ponatinib at a starting dose of 30mg/d in patients with CP-CML, following failure or intolerance of prior 1st line TKI therapy. The reduced starting dose is expected to have an improved toxicity profile compared to 45mg/d from other trials.

Methods:

The study population consists of 54 patients not younger than 18 years of age suffering from CP-CML, following failure or intolerance of prior first-line TKI therapy. Major exclusion criteria are any first-line anti-CML treatment other than TKI (apart from therapy with hydroxyurea) as well as any second-line therapy with a TKI (also for intolerance in 1stL); NYHA cardiac class 3-4 heart disease or cardiac symptoms within the last 12 months prior to recruitment; uncontrolled hypertension; a history of pancreatitis; pregnant or breast-feeding women; and patients who suffer from uncontrolled psychiatric disorders.

Starting with an initial dose of 30mg/d Ponatinib, dose adjustments will be made regarding to the response of individual patients, eg. after a patient has reached a major molecular response (MMR), a dose reduction to 15mg/d can be considered.

The primary endpoint is to estimate the proportion of CP-CML patients attaining MMR by 12 months of treatment.

The key secondary outcomes will be the rate and the time-to-toxicity, whereas “toxicity” is defined as any grade 3 or 4 drug-related adverse event that is not responsive to standard therapeutic management and requires treatment discontinuation. Further outcome measures are to evaluate the duration of MMR, and rate and time to transformation to accelerated phase or blastic phase of CML. In addition the evaluation of the duration and time to hematologic, cytogenetic and molecular responses will be determined.

Due to the high importance of AOEs the identification of potential risk factors and/or clinical surrogates and monitoring for these complications over the follow up period of 24 months is an additional goal of this study.

Results:

The cumulative safety data of the first five patients with median follow-up of appr. 8 months will be presented: In the first Development Safety Update Report no serious adverse event (SAE) has been documented during the conduct of the PONS trial from start of the study up to the end of the current reporting period.

Summary/Conclusion:

This study is open for recruitment

CML AdvocatesNetwork

(PB1972) PREVALENCE OF IMATINIB RESISTANCE IN CHRONIC MYELOID LEUKEMIA (CML): EXPERIENCE FROM A TERTIARY CARE CANCER CENTRE IN EASTERN INDIA

Debmalya Bhattacharyya*[1], R N Ghosh[1], Partha Pratim Gupta[1], Arnab Gupta[2], Shravasti Roy[3], Susanta Roychoudhury[2], Somsubhra Nath[2]
[1]Hemato-oncology, Saroj Gupta Cancer Centre and Research Institute, Kolkata, India, [2]Research and Molecular Biology, Saroj Gupta Cancer Centre and Research Institute, Kolkata, India, [3]Pathology and Laboratory Service, Saroj Gupta Cancer Centre and Research Institute, Kolkata, India

Background:

The management of Chronic Myeloid Leukemia (CML) has seen a paradigm shift with advent of the therapy with tyrosine kinase inhibitor (TKI), imatinib. Despite a high remission rate, a significant proportion of patients showed resistance and/or intolerance to imatinib therapy. However, the evidence of TKI failure of CML in the Eastern part of India remains elusive. To decipher the incidence of resistance to TKI after years of therapy, we performed a study in a tertiary cancer care centre, serving patients from Eastern Indian regions. Based on the CML cases registered at the centre for the last 13 years, we performed a longitudinal assessment of the disease history and clinical management, to portray the incidence of imatinib resistance in CML patients.

Aims:

This study aims to assess the prevalence of Imatinib resistance in treated CML patients from Eastern Indian cohort.

Methods:

The details of treated patients with CML have been collected from the institutional data record. Details of treatment with Imatinib were taken into account. Patients who were having loss of major molecular response (MMR) were identified. Mutation study of BCR-ABL kinase domain (KD) was done by Sanger sequencing. Calculation of type and incidence of KD mutation was done. The survival analyses were performed by Kaplan-Meier method.

Results:

The results are presented in tabular form as below:

CML cases (2005-2017)	Median period of Imatinib treatment	Loss of MMR (BCR-ABL >1.0%)	BCR-ABL KD mutation testing (no. of patients)	BCR-ABL KD mutation	Imatinib failure but no detectable BCR-ABL KD mutation on Sanger Sequencing
986	26 months	101	61	45 (73.8%)	16 (26.2%)

After years of therapy, KD mutations are seen in >70% of resistant patients.The survival analysis showed significant difference between treatment-sensitive and treatment–resistant pools.

Summary/Conclusion:

The increase of imatinib resistance is detected in Eastern-Indian region after long term therapy with imatinib. However, the full scenario couldnot be depicted due to resource constraints (affordability of patients and lack of next generation sequencing facility in many places). More patients are to be tested to achieve robust evidence along with analysis with specific mutations associated.