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ORIGINAL ARTICLE

# Chronic myeloid leukemia patients in Tunisia: epidemiology and outcome in the imatinib era (a multicentric experience)

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## Abstract

Data are limited in developing countries regarding the clinicopathologic features and response to therapy of chronic myeloid leukemia (CML) in the era of imatinib (IM). The objective of this study is to report on the clinicoepidemiologic features of CML in Tunisia, to evaluate the long-term outcome of patients in chronic (CP) or accelerated phase (AP) treated with IM 400 mg daily as frontline therapy, and to determine imatinib's efficacy and safety. From October 2002 to December 2014, 410 CML patients were treated with IM in six Tunisian departments of hematology. Response (hematologic, cytogenetic, and molecular responses) and outcome—overall survival (OS), event-free survival (EFS), and progression-free survival (PFS)—were evaluated. The following prognostic factors were analyzed for their impact on the European leukemia net (ELN) response, OS, EFS, and PFS at 5 years: age, sex, leukocyte count, Sokal score, European Treatment and Outcome Study (EUTOS) score, CML phase, time to starting IM, and impact of adverse events. The median age was 45 years (3–85 years). Two hundred ten (51.2%) patients were male. Splenomegaly was present in 322 of the 410 (79%). Additional cytogenetic abnormalities were encountered in 25 (6.3%) patients. At diagnosis, 379 (92.4%) patients were in CP, 31 (7.6%) were in AP. The Sokal risk was low in 87 (22.5%), intermediate in 138 (35.7%), and high in 164 patients (41.9%). The EUTOS risk was low in 217 (74%), and high in 77 (26%) patients. The rates of cumulative complete cytogenetic response (CCyR), major molecular response (MMR), and molecular response 4/5 log (MR4.5) in CP/AP-CML patients were 72, 68.4, and 46.4%, respectively. The median time to reach CCyR, MMR, and MR4.5 was 6 months (3–51), 18 months (3–72), and 24 months (3–100), respectively. According to the ELN criteria, optimal, suboptimal response, and failure were noted in 206 (51.8%), 61 (15.3%), and 125 (31.4%) patients, respectively. Five-

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year event-free survival (EFS), progression-free survival (PFS), and overall survival (OS) were 81, 90, and 90%, respectively. By multivariate analysis, AP, high EUTOS risk, and baseline WBC ≥ 150G/l remained independent predictive factors of non-optimal response to IM. The adverse events (AE) of IM were moderate and tolerable. With the caveats that the monitoring of the disease was not optimal, response rates were similar to those reported in previous studies. It is clear to us that improvements should be made in treatment of AP-CML and high Sokal risk group of CP-CML. The frontline use of second-generation tyrosine kinase inhibitor (TKI) is expected to improve the results of the first-line treatment of these high-risk Tunisian patients, but cost and accessibility of this therapy remain the problems in developing countries.

**Keywords** Tunisia · Clinical practice · CML · Imatinib · Management · Survey

## Introduction

Development of the drug imatinib (IM) is a crucial step in the treatment of patients with CML, especially in the chronic phase of the disease. Data are limited in developing countries regarding the clinicopathologic features and response to therapy in the era of IM [1, 2]. In Tunisia, CML patients were treated with IM from 2002. The primary objective of this study is to optimize CML management for Tunisian patients, as second-generation tyrosine kinase inhibitors (TKIs) are incorporated into clinical practice in 2008. Second objectives are to report on the clinicoepidemiologic features of CML in Tunisia, to evaluate the long-term outcome of patients in chronic (CP) or accelerated phase (AP) treated with IM 400 mg daily as frontline therapy, and to determine imatinib's efficacy and safety.

## Methods

### Study design

It is a retrospective, multicenter (6 Tunisian departments of hematology), non-randomized study. We collected the demographics, clinical data, and outcomes of all the Ph+ and or BCR-ABL+ CML patients in CP or AP treated between October 2002 and December 2014 with IM 400 mg daily as frontline therapy.

Patients were generally treated according to international guidelines; IM and molecular monitoring are accessible to patients covered by national insurance. For other CML patients without national insurance, IM was provided at no cost and regular monitoring indefinitely, under the Glivec International Patients Assistance Program (GIPAP) since 2007.

### Definitions, therapy, and monitoring response

CML phase definitions were according to the World Health Organization (WHO) criteria [3]. CP-CML was defined as the presence of < 5% blasts, 15–19% basophils, < 30% blasts, and promyelocytes in PB, and no extramedullary blastic disease. The accelerated phase (AP) was defined as 15 to 20% blasts in PB or BM, ≥ 20% basophils in PB or BM, thrombocytopenia < 100 × 109/L, and ≥ 30% blasts and promyelocytes in BM. The Sokal and European Treatment and Outcome Study (EUTOS) scores were used to subcategorize the CML patients into risk groups.

The IM was given at 400 mg orally every day. The median prescription delay was 2 months. Monitoring response was defined as the ELN-provided guidelines [4–6]. All patients have access to conventional cytogenetics. The karyotyping results reported the number of Ph-positive metaphases out of at least 20 metaphases. In situ hybridization with fluorescence (FISH) was used to detect BCR-ABL for diagnosis, especially when cytogenetics is negative or when no metaphase cells can be obtained. Qualitative RT-PCR (reverse transcription polymerase chain reaction) analysis for the detection of bcr-abl fusion transcripts was started in 2003. The type of bcr-abl transcript was determined via multiplex RT-PCR from cDNA synthesized from total leukocyte RNA at diagnosis. bcr-abl/abl ratio was determined by quantitative RT-PCR from cDNA since 2005 and standardized according to the international scale since 2009.

The molecular monitoring was based on peripheral blood samples for real-time quantitative polymerase chain reaction collected after 3, 6, and 12 months and every 6 months thereafter. Molecular responses have been defined according to the updated European leukemia net recommendations 2013; the molecular response was defined as major molecular response (MMR) if the bcr-abl /abl ratio was ≤0.1%; MR4 if the bcr-abl /abl ratio was ≤0.01%; MR4.5 if the bcr-abl/abl ratio was ≤ 0.0032%.

Response (hematologic, cytogenetic, and molecular responses) and outcome—overall survival (OS), event-free survival (EFS), and progression-free survival (PFS)—were evaluated. An event is defined either by a (molecular, cytogenetic, or hematologic) relapse, or by a disease progression to accelerated phase or blast phase CML, or by a death. Hematologic and non-hematologic grades 1 to

4 toxicities were evaluated at each follow-up. Adverse events were assessed using Common Terminology Criteria for Adverse Events.

The following prognostic factors were analyzed for their impact on ELN response, OS, EFS, and PFS at 5 years: age, sex, leukocyte count, Sokal score, EUTOS score, CML phase, time to starting IM, and impact of adverse events.

## Statistical analysis

Kaplan-Meier estimates were used to calculate the survival curves, and the curves were compared by using the log-rank test at $p$ 0.05 significant level. Univariate analysis using the $\chi 2$ test was done to assess for prognostic factors. Multivariate analysis based on Cox proportional hazards regression model was performed to select disease characteristics that contributed significantly to prognosis.

**Table 1** Patient demographics and baseline disease characteristics

| | *N* | % |
|---|---|---|
| Median age at diagnosis (range) | 45 years (3–85) | |
| Gender | | |
| M | 210 | Sex ratio |
| F | 200 | 1.05 |
| Asymptomatic patients at diagnosis | 168/388 | 44% |
| Spleen enlargement | 322 | 79% |
| Spleen size below costal margin (range, cm) | 12 | 1–35 |
| Median WBC rate (range) | 149 G/L | (5.39–860) |
| Additional cytogenetic abnormalities | 25/393 | 6.3% |
| Types of additional cytogenetics abnormalities | +8 (8 patients), −Y (3 patients), +ph, del11q, Del13q, del15q, del21q, +7, iso17q, +ph and *t*(1.8), *t*(1.15), *t*(4.9), *t*(9,15,22), *t*(9,12,22), *t*(3,9,22), *t*(9,7,22) | |
| CML phase | | |
| Chronic | 379 | 92.4% |
| Accelerated | 31 | 7.6% |
| Sokal score (387 pts) | | |
| Low | 87 | 22.5% |
| Intermediate | 138 | 35.6% |
| High | 162 | 41.9% |
| EUTOS score (294 pts) | | |
| Low | 217 | 74% |
| High | 77 | 26% |

*+8* trisomy 8, *−Y* loss of Y chromosome, *del* deletion, *+7* trisomy7, *i(17q)* isochromosome (17q), *+Ph* second Philadelphia chromosome

**Table 2** IM response

| | Evaluable pts | *N* | % |
|---|---|---|---|
| CHR (3 M) | 397 pts | 362 | 91.2 |
| CCyR (6 M) | 285 pts | 129 | 45.3 |
| CCyR (12 M) | 271 pts | 172 | 63.5 |
| MMR (18 M) | 266 pts | 140 | 52.6 |

# Results

## Patients characteristics

From October 2002 to December 2014, 410 CML patients were enrolled, in six hematology departments, among 714 CML patients diagnosed during the same period in Tunisia. The median follow-up duration was 72 months (12–255). Patient demographics and clinical variables are summarized in Table 1.

## Therapeutic results

The rate of cumulative complete hematologic response (CHR), complete cytogenetic response (CCyR), major molecular response (MMR), and molecular response 4/5 log (MR4.5) in CP/AP-CML patients were 91.4, 72, 68.5, and 46.1%, respectively. The median time to reach CCyR, MMR, and MR4.5 was 6 months (3–51), 18 months (3–72), and 24 months (3–100), respectively. IM response is summarized in Tables 2 and 3.

CCyR at 12 M and cumulative CCyR in CP-CML were 66.5 and 74.3%, respectively. According to the ELN criteria, 392 CML patients were evaluable. Optimal, suboptimal response, and failure were noted in 206 (52.5%), 61 (15.6%), and 125 (31.9%) patients, respectively. By multivariate analysis, AP, high EUTOS risk, and baseline WBC ≥ 150G/l remained independent predictive factors of non-optimal response to IM (Table 4).

Median follow-up was 72 months (12–255). Four hundred seven CML patients were evaluable for event survival. Molecular, cytogenetic, and hematologic relapse was noted in 5, 2, and 3%, respectively. Five-year event-free survival (EFS), progression-free survival (PFS), and overall survival (OS) were 81, 90, and 90%, respectively (Fig. 1).

**Table 3** Cumulative CCyR, MMR, and MR4.5 to IM

| | Evaluable pts | % | Median delay (months) |
|---|---|---|---|
| CCyR | 369 pts | 73 | 6 (3–51) |
| MMR | 304 pts | 68.4 | 18 (3–72) |
| MR4.5 | 289 pts | 46.4 | 24 (3–100) |

**Table 4** Predictive factors of non-optimal response to IM by multivariate analysis

| | *p* | Adjusted odds ratio |
|---|---|---|
| GB > 150 G/l | 0.001 | 2.27 |
| AP | 0.005 | 6.25 |
| High EUTOS score | 0.02 | 2.01 |

Table 5 summarized predictive factors of PFS, EFS, and OS by univariate and multivariate analysis. AP was an adverse independent prognostic factor for EFS, PFS, and OS.

Forty-one deaths occurred during the study period. The causes of death included 29 following an acute transformation, 1 acute myocardial infarction, and not specified in 10 patients.

Patients that obtained CCyR at 12 months after the initiation of IM treatment were associated with longer PFS (97 vs 76%; $p < 0.0001$) and OS (99 vs 74%; $p < 0.0001$) (Fig. 2). ELN response was also significantly associated with better EFS ($p < 0.0001$) and OS ($p < 0.0001$).

## Safety profile

The adverse events (AE) of IM were assessed in 377 patients. They were moderate and tolerable. The frequencies of AE that were attributable to imatinib are summarized in Table 6. Only 16 patients discontinued IM for intolerance. IM-related hematologic AE (21.7%) included neutropenia in 9%, anemia in 8%, thrombocytopenia in 14%, and pancytopenia in 3%. Grade 3/4 hematologic AE were noted in 1.06% for neutropenia, 2.3% for anemia, and 3.4% for thrombocytopenia. Non-hematologic AE (19%) were mainly grade 1/2, including edema in 6.1%, weight gain in 5.5%, digestive disorders, and skin rash in 4.7 and 3.1%, respectively.

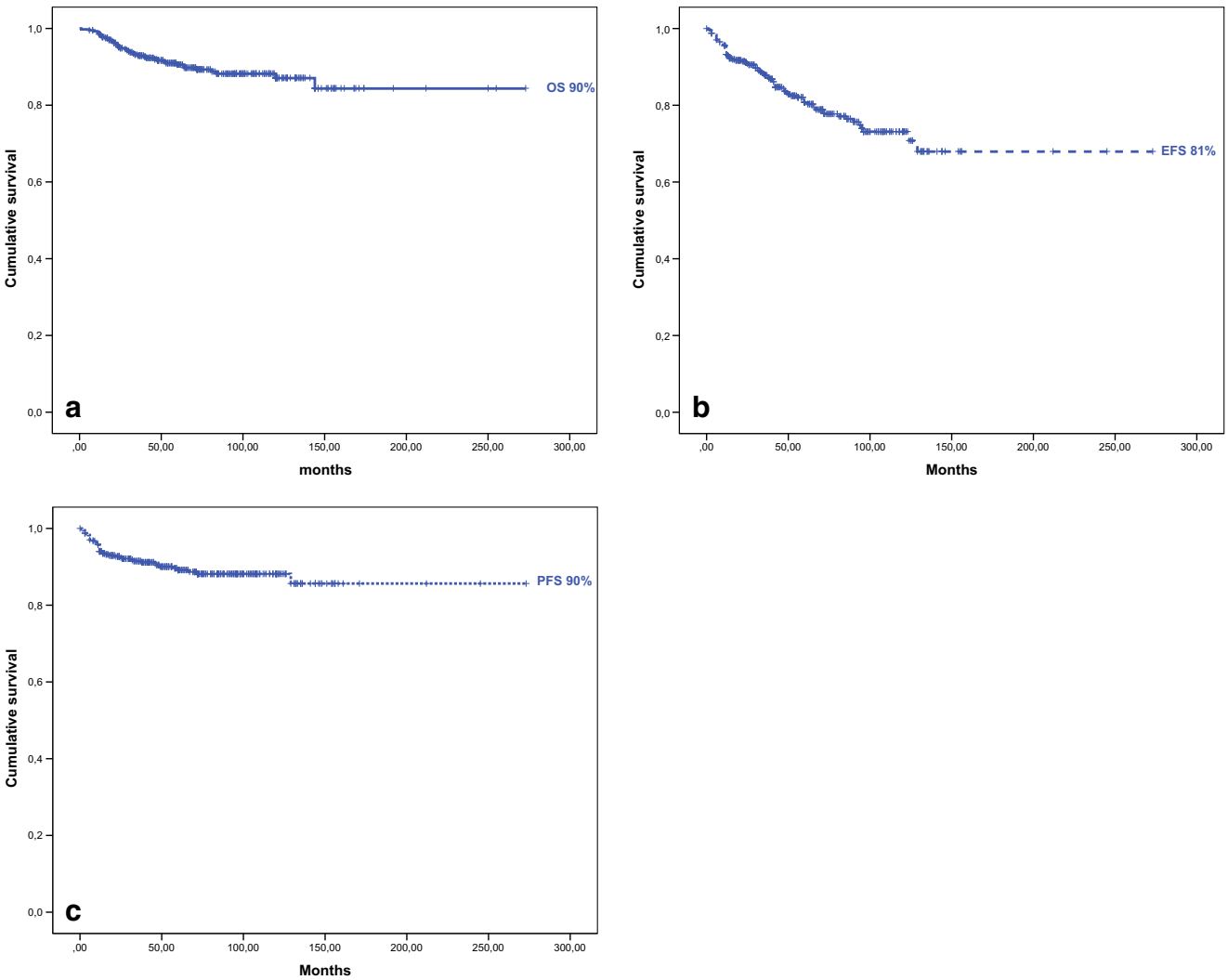


**Fig. 1** Survival in newly diagnosed CP-CML. **a** OS. **b** EFS. **c** PFS

**Table 5** Predictive factors of PFS, EFS, and OS by univariate and multivariate analysis

| | | PFS | | | EFS | | | OS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | % | *P* (univariate) | *P* (multivariate) | % | *P* (univariate) | *P* (multivariate) | % | *P* (univariate) | *P* (multivariate) |
| Sokal score | High interm/low risk | 87/98 | 0.003 | | 77/89 | 0.005 | | 87/98 | 0.004 | |
| CML phase | CP/AP | 92/68 | < 0.0001 | 0.006 | 82/68 | 0.004 | 0.035 | 92/71 | < 0.0001 | 0.005 |
| CIII(3 M) | Yes/no | 92/61 | < 0.0001 | 0.028 | 83/53 | < 0.0001 | | 93/67 | < 0.0001 | |
| CCyR(6 M) | Yes/no | 97/83 | < 0.0001 | | 90/70 | < 0.0001 | 0.022 | 98/85 | < 0.0001 | |
| CCyR(12 M) | Yes/No | 97/76 | < 0.0001 | < 0.0001 | 89/62 | < 0.0001 | | 99/74 | < 0.0001 | < 0.0001 |
| MMR (18 M) | Yes/no | 96/83 | < 0.0001 | | 88/68 | < 0.0001 | | 97/83 | < 0.0001 | |
| ELN response | Op/Sub/Fail | 97/95/74 | < 0.0001 | | 92/77/62 | < 0.0001 | 0.004 | 97/95/75 | < 0.0001 | 0.02 |

## Discussion

Our study is a multicenter analysis describing demographic, clinical features, and IM response in Tunisian CML patients over a period of 10 years. Tunisian incidence data for CML are lacking. Like the descriptions from developing countries, the median age in our study was 45 years. Data published in SEER cancer indicated a median age much older [7]. Several explanations were suggested for this difference in median ages, including shorter life expectancy, under diagnosis in the geriatric population, and differences in the age structures of the populations [8, 9]. The observed male gender of Tunisian CML patients is similar to that reported elsewhere.

Similar to studies in developed countries, about 50% of patients are asymptomatic at time of diagnosis and 92.4% were found in CP-CML [2].

Compared with developed countries, we found that substantial number of patients in our series were high-risk Sokal group. This might be because of late presentation and delay in the diagnosis. At the time of presentation, about 80% of patients had an enlarged spleen. Moreover, the median size of the spleen at the time of diagnosis is 12 cm (1–35).

Access to IM has a major impact on the successful management and increasing prevalence of patients living with CML. Fortunately, thanks to the national insurance and the GIPAP program for poorer patients, IM is free in Tunisia and we are able to give IM to all of our patients with no dose interruptions.

The response to IM in our patients is slightly lower than that observed in patients from high-resource countries. In fact, CCyR at 12 M and cumulative CCyR in

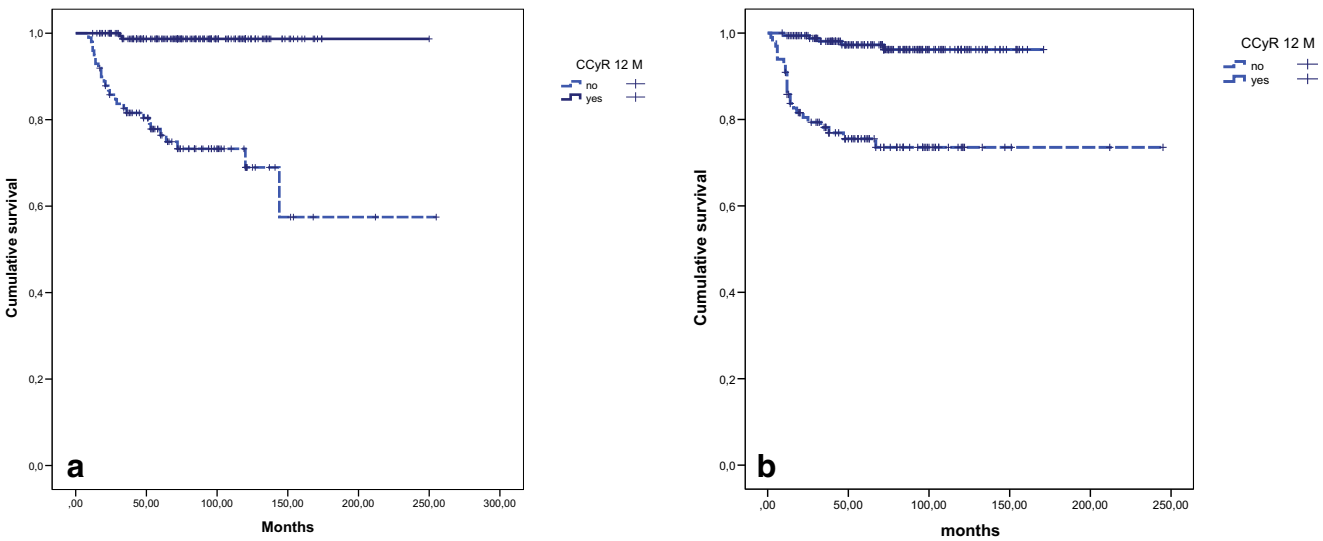


**Fig. 2** OS and PFS according to CCyR at 12 M

**Table 6** Hematologic AE (21.7%) and non-hematologic AE (19%)

| | *n* | % |
|---|---|---|
| Neutropenia | 34 | 9 |
| Anemia | 30 | 8 |
| Thrombocytopenia | 53 | 14 |
| Pancytopenia | 13 | 3 |
| MDS | 1 | 0.26 |
| Edema | 23 | 6.1 |
| Weight gain | 21 | 5.5 |
| Digestive disorders | 18 | 4.7 |
| Cutaneous AE | 12 | 3.1 |
| Arthralgia | 5 | 1.3 |
| Myalgia | 5 | 1.3 |
| Hepatic AE | 4 | 1.06 |
| Pancreatitis | 1 | 0.26 |
| Gynecomastia | 1 | 0.26 |
| Breast cancer | 1 (18 M) | 0.26 |
| Lung cancer | 1 (6 M) | 0.26 |

CP-CML were 66.5 and 74.3%, respectively. The original IRIS study reported a CCyR of 73.8% [10] but with a best cumulative CCyR at 5 years of 87% in previously untreated patients in CP-CML [11]. Kantarjian et al. described a very similar CCyR of 81% in his group of patients with CP-CML [12]. Only 52.5% percent of CP-AP-CML reached optimal response. Three independent predictive factors for optimal response were identified: CP-CML, low EUTOS score, and WBC $< 150{,}000/mm^3$. The diagnosis of the disease in the late chronic phase with an important proportion of high-risk CML patients may explain this response. Rodrigues Lemos et al. have proved the interdependence of late diagnosis and delayed treatment on long-term sustained optimal response to IM therapy [13]. Regarding the EUTOS score using the percentage of basophils and spleen size, Hasford et al. had shown that it best discriminated between high-risk and low-risk groups of patients, with a positive predictive value of not reaching a CCyR of 34% [14]. The score can be used to identify CML patients with significantly lower probabilities of responding to therapy and survival, thus alerting physicians to those patients who require closer observation and early intervention [14, 15].

Before the TKIs era, the Sokal score has been used to predict outcome in CML patients. Recent results suggest that this score is unsuitable in predicting OS and CCyR of CP-CML patients on IM, as compared to their usefulness before the IM era [16].

Survivals in CP-CML patients were similar to those reported by others [10, 17], but survival in AP-CML patients is lower than that in the literature and AP was an adverse independent prognostic factor for EFS, PFS, and OS. CCyR at 12 months was associated with longer PFS and OS. ELN response was also significantly associated with EFS.

In fact, achievement of CCyR is a widely accepted goal for CML therapy because cytogenetic responses have been shown to be a significant predictor for survival [6, 11, 18]. In our study, CCyR (12 M) was associated with better PFS and OS. Thus, molecular monitoring is markedly more sensitive than conventional cytogenetic and is able to routinely detect much lower levels of disease. Molecular response has been found to be predictive of the duration and loss of CCyR, PFS, and EFS. Based on the German CML study IV, MMR at 12 months was associated with significantly better PFS and OS at 3 years compared with no MMR. Achievement of at least a MMR is the predominant treatment goal in CP-CML [19].

It is now well established that patients with chronic myeloid leukemia in chronic phase who achieve early molecular response (EMR: defined as BCR-ABL $\leq 10\%$ on the international scale at 3 or 6 months) have improved outcomes. Patients who achieve these responses have an improved probability of achieving a favorable progression-free survival and OS [20, 21].

Similar to data in other studies, adverse events to IM are manageable and occasionally may lead to discontinuation of drug. The most frequent grades 3 and 4 hematologic toxicity in this analysis was thrombocytopenia (14%).

Coming from a developing country, our results are acceptable. Nevertheless, we realize that our study has several weaknesses. Molecular and cytogenetic monitoring is missing in some patients. Availability of laboratory tests varies considerably between regions. Optimizing the management should be considered especially in patients with accelerated phase. Predictive factors can be used to select patients who require second-generation TKI on frontline.

**Conclusion** In summary, based on this 10-year analysis, we found that substantial number of patients in our series were in intermediate- or high-risk group. With the caveats that the monitoring of the disease was not optimal, response rates were similar to those reported in previous studies, with minimal side effects. It is clear to us that improvements should be made in treatment of AP-CML and high-risk Sokal group of CP-CML. The frontline use of second-generation TKI is expected to improve the results of the first-line treatment of these high-risk Tunisian patients, but cost and accessibility of this therapy remain the problems in developing countries.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References


1. Aziz Z, Iqbal J, Akram M, Saeed S (2007) Treatment of chronic myeloid leukemia in the imatinib era perspective from a developing country. Cancer 109(6):1138–1145. https://doi.org/10.1002/cncr.22498
2. Dong-Wook K, Shripad DB, Udomsak B et al (2010) Chronic myeloid leukemia in the Asia-Pacific region: current practice, challenges and opportunities in the targeted therapy era. Leuk Res 34: 1459–1471
3. Cortes JE, Talpaz M, O'Brien S et al (2006) Staging of chronic myeloid leukemia in the imatinib era: an evaluation of the World Health Organization proposal. Cancer 106(6):1306–1315. https://doi.org/10.1002/cncr.21756
4. Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, Apperley J, Cervantes F, Cortes J, Deininger M, Gratwohl A, Guilhot F, Horowitz M, Hughes T, Kantarjian H, Larson R, Niederwieser D, Silver R, Hehlmann R, European LeukemiaNet (2006) Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European Leukemia Net. Blood 108(6):1809–1820. https://doi.org/10.1182/blood-2006-02-005686
5. Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silver RT, Goldman J, Hehlmann R, European LeukemiaNet (2009) Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. JCO 27(35):6041–6051. https://doi.org/10.1200/JCO.2009.25.0779
6. Baccarani M, Deininger MW, Rosti G et al (2013) European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 122(6):872–884. https://doi.org/10.1182/blood-2013-05-501569
7. Rohrbacher M, Hasford J (2009) Epidemiology of chronic myeloid leukaemia. Best Pract Res Clin Haematol 22(3):295–302. https://doi.org/10.1016/j.beha.2009.07.007
8. Funke VA, Medeiro CR, Lima DH et al (2005) Therapy of chronic myeloid leukemia with imatinib mesylate in Brazil: a study of 98 cases. Rev Bras Hematol Hemoter 27:159–165
9. Aguayo A, Garcia-Alvarez E, Cazares-Ordonez Y, Crespo-Solis E, Martinez-Baños D, Guadarrama-Beltran E, Cervera-Ceballos EE, Lopez-Karpovitch X (2008) Chronic myeloid leukemia: a clinicoepidemiologic and therapeutic description of a single institution in Mexico City. Clin Leuk 2(4):261–266. https://doi.org/10.3816/CLK.2008.n.036
10. O'Brien SG, Guilhot F, Larson RA et al (2003) Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 348(11): 994–1004. https://doi.org/10.1056/NEJMoa022457
11. Druker BJ, Guilhot F, O'Brien SG et al (2006) Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 355(23):2408–2417. https://doi.org/10.1056/NEJMoa062867
12. Kantarjian HM, O'Brien S, Cortes J et al (2003) Imatinib mesylate therapy improves survival in patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia in the chronic phase: comparison with historic data. Cancer 98(12): 2636–2642. https://doi.org/10.1002/cncr.11831
13. Rodrigues Lemos JA, Quinto Bentes A, Simões Beltrão AC et al (2010) Late diagnosis and delayed treatment combined as a cause of suboptimal response to imatinib in chronic myeloid leukemia in developing countries, 116. Blood, Dent Abstr 4750
14. Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, Guilhot F, Porkka K, Ossenkoppele G, Lindoerfer D, Simonsson B, Pfirrmann M, Hehlmann R (2011) Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood 118(3):686–692. https://doi.org/10.1182/blood-2010-12-319038
15. Zelada J, Capurro MPA, Rojas B et al (2013) Is EUTOS score predictive of outcome in patients with early chronic phase chronic myeloid leukemia treated with imatinib? Preliminary data from the National Protocol of the Chilean Cooperative Group Panda. Blood 122(21):5196
16. Oyekunle AA, Osho PO, Aneke JC et al (2012) The predictive value of the Sokal and Hasford scoring systems in chronic myeloid leukaemia in the imatinib era. J Hematol Malig 2:25–32
17. Tauchi T, Kizakib M, Okamotoc S et al (2011) Seven-year follow-up of patients receiving imatinib for the treatment of newly diagnosed chronic myelogenous leukemia by the TARGET system. Leuk Res 35(5):585–590. https://doi.org/10.1016/j.leukres.2010.10.027
18. Kantarjian HM, Larson RA, Cortés JE, Deering KL, Mauro MJ (2013) Current practices in the management of chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk 13(1):48–54. https://doi.org/10.1016/j.clml.2012.07.009
19. Hehlmann R, Lauseker M, Jung-Munkwitz S, Leitner A, Müller MC, Pletsch N, Proetel U, Haferlach C, Schlegelberger B, Balleisen L, Hänel M, Pfirrmann M, Krause SW, Nerl C, Pralle H, Gratwohl A, Hossfeld DK, Hasford J, Hochhaus A, Saußele S (2011) Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-$\alpha$ in newly diagnosed chronic myeloid leukemia. J Clin Oncol 29(12):1634–1642. https://doi.org/10.1200/JCO.2010.32.0598
20. Lapusan S, Yong A, Savani BN et al (2014) Achieving early molecular response in chronic myeloid leukemia in chronic phase to reduce the risk of progression: clinical relevance of the 3- and 6-month time points. Eur J Haematol 95:103–111
21. Jain P, Kantarjian H, Nazha A, O'Brien S, Jabbour E, Romo CG, Pierce S, Cardenas-Turanzas M, Verstovsek S, Borthakur G, Ravandi F, Quintas-Cardama A, Cortes J (2013) Early responses predict better outcomes in patients with newly diagnosed chronic myeloid leukemia: results with four tyrosine kinase inhibitor modalities. Blood 121(24):4867–4874. https://doi.org/10.1182/blood-2013-03-490128


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