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# OVERVIEW OF CHRONIC MYELOID LEUKEMIA PATIENTS IN THE HOLY CITY OF KARBALA

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## ABSTRACT

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder characterized by presence of Philadelphia chromosome. Over time CML treatment has change dramatically; especially when Tyrosine Kinase Inhibitor (TKI) introduced, which significantly increase survival and improve quality of life for all patients especially when it's associated with good drug adherence and sequential response monitoring to TKI. **Aim:** To study the characteristics of CML patient's in the Holy City of Karbala and the outcome of Tyrosine Kinase Inhibitor in control of their disease. **Method:** The present descriptive study included 56 patients, conducted in Al Imam Al Hussein Hematology/Oncology center at the Holy city of Karbala in Iraq from June 2017 - June 2018. Data from patients with CML were collected and critically analyzed for the demographic data, type of treatment they used and their compliance to drug. **Results:** The median age was 46 years; male-to-female ratio was 1.24:1. 96.4% patients were diagnosed in chronic phase of their disease. Major molecular response achieved in 79% (27/34) of patients on Gleevec. 37.5% patients were switch to Tasigna after Imatinib resistant or intolerance, 52% of them achieved major molecular response. Drug adherence found in 68% (38/56) patients. **Conclusion:** CML slightly male predominance, diagnosed at age younger than that report in the United States and Europe, response to TKI nearly similar to that report in international study. Drug

adherence and sequential monitoring of patients can improve therapeutic effect of TKI therapy.

**KEYWORD:** Chronic myeloid leukemia, Philadelphia chromosome, BCR-ABL, Imatinib, Nilotinib, Drug adherence.

## INTRODUCTION

CML is a clonal disorder of hematopoietic stem cells, Characterize by identification of Philadelphia (Ph) chromosome which produces as result of reciprocal translocation between chromosomes 9 and 22 [t(9;22)]. This translocation results in the transfer of the Ableson (ABL) gene on chromosome 9 to an area termed the breakpoint cluster region (BCR) on chromosome 22, resulting in the BCR-ABL fusion gene. This fusion gene results in the expression of the constitutively active protein tyrosine kinase (BCR-ABL1) which is the main key in pathogenesis of CML.[1,2]

In 1960, The Ph chromosome was identified. After that detection of BCR-ABL1 at 1985, this made CML the first disease defined on a molecular basis.[3]

The incidence of CML range between 10 and 15 cases/$10^6$/year. CML represents 0.5% of all new cancer cases in the United States which account for 15% of adult leukemia.[4,5] The median age at diagnosis in Europe range between 60 and 65 years, but it considerable lower in countries with younger population.[6]

Most patients are diagnosed in the indolent or chronic phase. If they not receive right treatment their disease may progress into the accelerated and blast phases, which are poor outcomes.[7] Treatment of CML has gone through a real revolution throughout the years. In the early 20th century Palliative splenic radiotherapy was used. Then, at 1960, Busulfan emerged, after that hydroxyurea was used. But, these agents was unable to suppress the Ph chromosome, and they were unable to change the natural history of the disease.[8]

At 1980 Interferon-α (IFN-α) based regimens was introduced. In chronic phase, the median survival with interferon- α was 6 to 7 years while on hydroxyurea was 3 to 4 years. Allogeneic stem cell transplantation (SCT) used in CML but is associated with higher rate of morbidity and mortality. Before emerging of TKI, Allogeneic SCT was a first line therapy among eligible patients, but now considered as a second- or third-line strategy in CML after failure of TKI therapy.[7]

Imatinib (Gleevec™) the first-generation TKI, a drug that targets BCR-ABL tyrosine kinase, received Food and Drug Administration (FDA) approval on May 10, 2001.[9] IRIS study (International Randomized Study of Interferon and STI571), approve that Imatinib was superior to IFN-α plus low-dose Cytarabine as first-line therapy in newly diagnosed chronic-phase CML.[10] However dramatic response were obtained with Imatinib, the results were not reliable among some patients who developed Imatinib resistance or intolerance. Newer drugs are being developed to overcome this problem. Mutational analysis should be performed in those with Imatinib failure, escalating BCR-ABL transcript levels and those with suboptimal response.[11]

Nilotinib, a selective BCR-ABL kinase inhibitor, is 30 times more potent than Imatinib at inhibiting most BCR-ABLmutations except T315I.[12,13]

Dasatinib is a second-generation BCR-ABL inhibitor that has 325-fold higher potency in vitro compared with Imatinib. Dasatinib 100 mg once daily showed durable efficacy and safety.[12,14] Imatinib, nilotinib, and dasatinib, and bosutinib are approved for first-line use. All therapies are very effective with excellent progressive free survival. Second generation TKIs induce faster cytogenetic and molecular responses, without any difference in overall survival between them and Imatinib.[5,15]

Imatinib is still the first-line TKI for many clinicians because its long-term side effect profile is well understood. Further, in most health systems, it is significantly cheaper than newer drug.[15] Hence, the present study aimed to assess the characteristics of CML patient's in the Holy City of Karbala and the outcome of Tyrosine Kinase Inhibitor in control of their disease.

## PATIENTS AND METHODS

A descriptive study conducted between June 2017 to June 2018 at Al Imam Al Hussein Hematology/Oncology center/ Al-Imam Al-Hussein Medical City at the Holy city of Karbala / Iraq. A total of fifty six chronic myeloid leukemia patients were enrolling in this study, all of them were confirm to have CML by demonstration of Philadelphia chromosome by fluorescence in situ hybridization (FISH) study and/or BCR-ABL fusion transcript by Quantitative real-time polymerase chain reaction(Q PCR) in addition to clinical and hematological finding. All of them receive tyrosine kinase inhibitor for one year or more.

Each patient was survey by self-administered questionnaire including basic demographic characteristic, type and side effect of treatment they used, their compliance to drug, family history of cancer, history of chronic illness and drug used. Medical data of patients collected by the doctor using patient's medical records and reports during time of study.

BCR-ABL fusion transcript by Q PCR was used for follow up and monitoring response to tyrosine kinase inhibitor. BCR-ABL transcripts were detected by analyzing peripheral blood with Q PCR according to the International Scale. Response to treatment was assessed according to the criteria for hematological and molecular response and relapse in National Comprehensive Cancer Network (NCCN) guidelines (version 1.2019) for chronic myeloid leukemia. Complete cytogenetic responses (CCyR) define as 2-log reduction in transcript levels or ≤1% IS (International Scale). Major molecularresponse (MMR) is defined as a 3-log reduction in transcript levelsor ≤0.1% IS, MR4 define as a 4-log reduction in transcript levelsor ≤0.01% IS. A complete molecular (CMR) define as ≥4.5-log reduction in transcript levelsor ≤0.0032% IS.[5]

Classification of disease to (chronic phase, accelerate phase and blast crisis) according to WHO classification of myeloid neoplasm and acute leukemia.[16] Molecular response to TKI dependent on the last result of Q BCR-ABL (last-time response) for each patient duo to most of patient's loss of sequential monitoring. Adherence to treatment evaluated by several way including: pill counted at each monthly visit and information was taken from patients or their family for compliance to treatment regarding time of treatment taken, use other drug may interact with treatment and any side effect that cause drug use interrupted or discontinue. Also, medical and pharmacological record was used to assess adherence of patients to drug during the period of their illness. Non adherence to drug defines: Patient with poor compliance to drug or have period of drug interrupted.

**Statistical Analysis:** All data analyzed using SPSS (version 20 software) computer program. Statistical analysis included descriptive statistics like: frequency tables and graphs, including: bar diagrams and pie chart.

The study done after agreement was taken from adult's patients and parents of child's patients. Also permission was taken from Al Imam Al Hussein Hematology/Oncology center.

## RESULTS

**Sex and Age:** A total of 56 patients of CML from Al- Imam Al- Hussein Hematology/ Oncology Center were enrolled in this study. Thirty one (55.4%) of them was male and twenty five (44.6%) were female; male-to-female ratio was 1.24:1. The baseline Demographic characteristics of enrolled patients are listed in Table 1.

**Table 1: Baseline Patients Characteristic.**

| GENDER | | |
|---|---|---|
| **Characteristic** | **Number** | **Percentage** |
| **Male** | 31 | 55.4% |
| **Female** | 25 | 44.6% |
| **OCCUPATION** | | |
| **House wife** | 22 | 39.3% |
| **Employee** | 15 | 26.8% |
| **Worker** | 11 | 19.6% |
| **Solder** | 2 | 3.6% |
| **Student** | 2 | 3.6% |
| **Driver** | 1 | 1.8% |
| **Child** | 3 | 5.3% |
| **EDUCATION** | | |
| **Collage** | 11 | 19.6% |
| **Secondary** | 12 | 21.4% |
| **Primary** | 27 | 48.2% |
| **Illiterate** | 3 | 5.4% |
| **Child** | 3 | 5.4% |
| **ADDRESS** | | |
| **Center of city** | 34 | 60.7% |
| **Al Husseinia** | 7 | 12.5% |
| **Al Hindia** | 8 | 14.3% |
| **Al Hur** | 4 | 7.1% |
| **En Al Tamor** | 3 | 5.4% |
| **PHASE** | | |
| **Chronic** | 54 | 96.4% |
| **Accelerate** | 2 | 3.6% |
| **Sum** | 56 | 100% |

The mean age of patients was 43 ± 16.19 years and the median age was 46 years.

The mean age of male was 43.87 ±15.1 years, higher than that of female 41.92 ± 17.69 years. Median age of male and female was 45 years, 47 years respectively. The age of the oldest patient was 70 years old male, while the youngest patient was 2 years female. Twenty eight (50%) patient their age between 45–64 years old. The most frequently diagnosed people aged

between 45-54 years, represented (26.7%). Pediatric patients (0-14 years) were 4 (7.1%) patients Figure 1.

**Duration of Disease**

Figure 2. Show 12 (21.4%) patients surviving with CML for ≥10 years and 20 (35.7%) patients were surviving with CML between (9-5) year.

**Family History of Cancer**

Thirteen (23.2%) patients had family history of different type of cancer other than CML and two patients were father and his son both of them has CML without any significant risk factor.

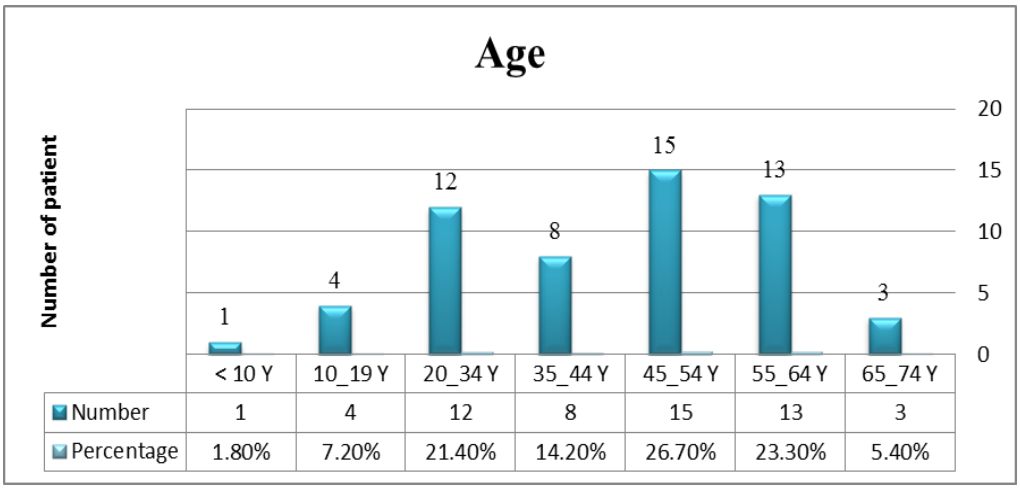


**Figure 1: Age Distribution in Chronic Myeloid Leukemia Patients.**

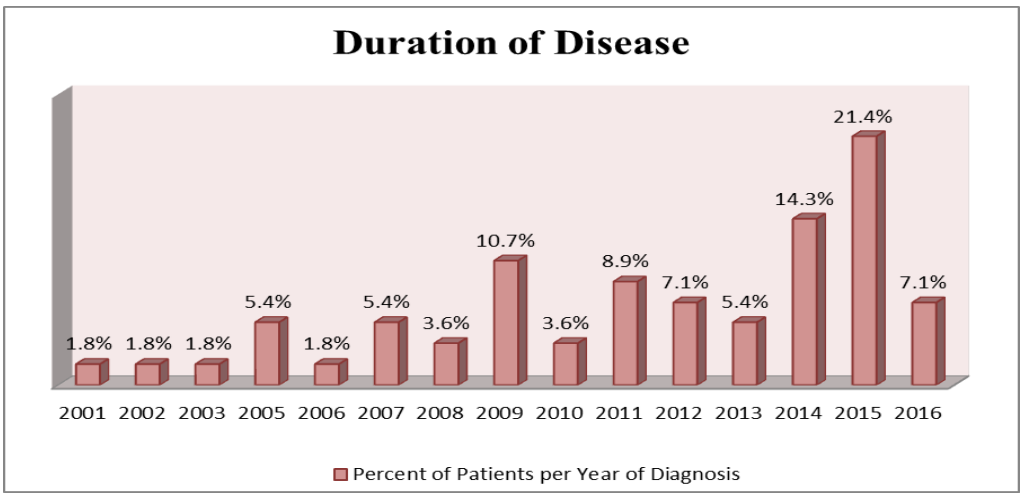


**Figure 2: Duration of Disease According to Year of Diagnosis.**

**Type of Treatment and Response**

Fifty four (96.4%) of patient were diagnosed in chronic phase of their disease and two (3.6%) patient presented with accelerated phase. First line TKI treatment for all patients was Imatinib, except 22 year old female she receives Nilotinib as first line treatment Figure 3.

Hematological response achieve in all patients after starting TKI (Imatinib, Nilotinib). Molecular response assessments were conducted less frequent than recommended.

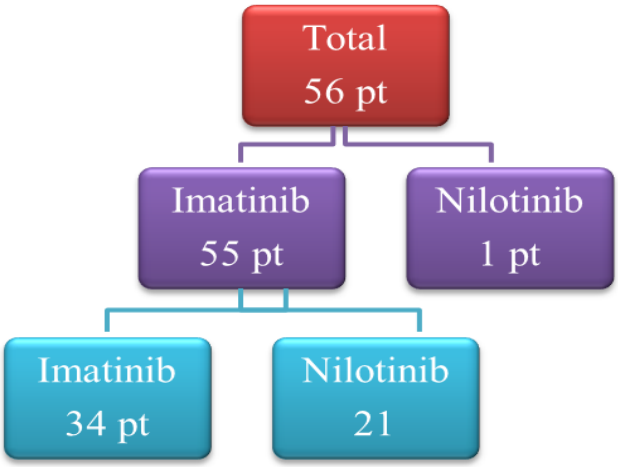


**Figure 3: Patients Distribution According to Line of Treatment They Used.**

**A. Imatinib:** Thirty four (60.7%) patients out of 56 were on Imatinib for more than one year. 27/34 (79%) of them achieve major molecular response [10/34 (29%) had deep molecular response]. BCR-ABL >10% found in two (5.9%) patients one of them loss of MMR duo to stop treatment for more than one year and 2 year age child Failure to achieve response duo to reluctant to treatment. Poor compliance to drug leads one patient to loss her response from MR5 to CCyR. One patient her disease was progressed to blast crisis after achieve MMR duo to poor compliance. Table 2.

**B. Nilotinib:** Twenty one (37.5%) patients out of 56 on Nilotinib 14 (66.7%) male and 7(33.3%) female. 16/21 (76%) patient switch to Tasigna because the fail to achieve CCyR, while 5/21 (24%) patients were Imatinib intolerance. only one patient start Nilotinib as a first line and achieve MR4 during first year of treatment.

MMR achieved in 11/21 (52%) patients. BCR-ABL >10% found in six patients (two with poor compliance to Nilotinib, two not tolerate it and two their disease progress). Also Loss of major molecular response observed in two patients Table 2.

**Patient Compliance to Treatment**

Drug adherence found in 38/56 (68%) patients, while treatment interruption and non-adherence to therapy was found in 18/56 (32%) patients [12/18 (21.4%) of them failure to archive target molecular response and need switch to second line of treatment].

**Table 2: Molecular Response to TKI Dependent on the Last Result of Q BCR-ABL (last-time Response).**

| Molecular Response in Patients on Imatinib and Nilotinib | | |
|---|---|---|
| **BCR-ABL** | **Patient on Imatinib** | **Patient on Nilotinib** |
| **>10%** | 2 (5.9%) | 6 (28.6%) |
| **10-1%** | 0 (0.0%) | 1 (4.7%) |
| **CCyR 0.1-<1%** | 1 (3%) | 2 (9.6%) |
| **MMR 0.1** | 14 (41.1%) | 5 (23.8%) |
| **MR4 0.01** | 3 (8.8%) | 3 (14.3%) |
| **MR4.5 0.0032** | 10 (29.4%) | 3 (14.3%) |
| **unknown** | 3 (8.8%) | 1(4.6%) |
| **Blast crisis** | 1 (3%) | 0(0%) |
| **Sum** | 34 | 21 |

**Adverse Event to Tyrosine Kinase Inhibitor**

**a. Imatinib:** Twenty four (43.63%) of patient on Imatinib complained from oedema and arthralgia and 23 (42%) their weight was increase. Sixteen (29%) patient presented with dermatological problem like (skin rash, itching, melasma). Gastrointestinal toxicity reported in 12 (22%) patients and eye problem found in 4(7.27%). But four patients presented with sever pancytopenia that lead to stop Gleevec and switch to Tasigna.

**b. Nilotinib:** Prolong QT interval with hypomagnesemia found in one patient need to stop drug and resume Nilotinib with dose reduction after corrected of hypomagnesemia. One patient developed ischemic heart diseases which need to stop Nilotinib. Hyperglycemia present in one patient control by oral hypoglycemic agent. One patient complains from sever Pancytopenia which lead to stop Nilotinib and switch to third line. Dermatological problem was record in three patients lead to treatment interrupted and dose reduction. Two patients complain from headache.

**DISCUSSION**

Chronic myeloid leukemia is uncommon, data from the Surveillance, Epidemiology, and End Results (SEER) program show that 0.2% of men and women will be diagnosed with chronic myeloid leukemia at some point during their lifetime. In Karbala city CML was the second

common type of leukemia after acute lymphoblastic leukemia, presenting more than 24% of cases. CML is more common in older adults and rare in children.[17,18,19]

In current study 92.9% of patients was adult. Whereas children represented 7.1% of patients which higher than reported in international study (2.7% of patients with CML diagnosed before 20 years old).[7]

The disease has a slight male predominance, male-to-female ratio was 1.24:1, correlated with United States [about 8,990 new cases will be diagnosed with CML 5,250 in men and 3,740 in women], Bangladesh 2:1 and Pakistan 1.6:1.[15,17,20,21] While in Babylon and Egypt the disease show female predominance 1:1.2, 1:1.7 respectively.[22,23]

According to SEER program, Chronic myeloid leukemia is most frequently diagnosed among people aged 65-74 years with median age at diagnosis in USA was 65 years.[17] In Europe the median age at diagnosis ranges between 60 and 65 years but it considerable lower in countries with a younger population.[19] The median age of patients in this study was 46 years while the mean age was 43 years, nearly similar to the mean age in the local study in Babylon 44 years. Also in India the median age was 40 years.[22,24] But median age of patients in Indonesia and Pakistan was 36 and 39 years respectively.[21,25] This could reflect the higher life expectancy in the more developed countries compared with less developed countries.[26]

There is no familial predisposing in CML, Diagnosis of patient with CML in relatives of patients with CML.[7] But we found two patient (father and his son were diagnosed with CML without any significant risk factors.

In Europe About 50% of patients with CML are asymptomatic at time of diagnosis and More than 90% of CML patients present in chronic phase; initial blast phase is unusual.[19] This strongly correlated with our data; (96.4%) of patient were diagnosed in chronic phase of their disease and two patient presented with accelerated phase.

Response to TKI therapy is determined by the measurement of hematological, cytogenetic and molecular response. The objective of TKI therapy is to reach a CCyR within 12 months of beginning of therapy and to avoid progression of disease to accelerated or blast phase.[5]

When CCyR is achieved, BCR-ABL1 transicripts remain detectable despite cytogenetic analysis become negative. QPCR use to monitoring molecular response after acheive CCyR.

QPCR is non-invasive test that only need peripheral blood sample without need to bone marrow aspirate.[5,15]

In IRIS study Achieving a major molecular response in complete cytogenetic response at 12 months was associated with estimated 5-year rates of transformation-free survival and survival rates of 100%.[7,27] Disappearance of *BCR-ABL* transcripts was initially observed in a minority of patients (5%) but is now reported with longer-term follow-up in 30% to 50% of patients. In general, a reduction of *BCR-ABL* transcripts by 4.5 log or more may reach levels below detection in most molecular laboratories.[7,28]

But from data of our patients we found that sequential monitoring of patients with QPCR didn't underwent at intervals that recommended for assess response to TKI, because either the patients live far from the specialized laboratories that perform Q BCR-ABL, or the test was expensive for patients, or not available, or patients poor compliance to monitoring, these lead to Loss of monitoring or delay form recommended time.

For that we assess response to Gleevec after one year or more from initiation of treatment (last-time response) duo to most of patient's loss of sequential monitoring. We found that major molecular response achieve in 79% (27/34) of patients on Gleevec and deep molecular response achieved in 29% (10/34) of them. Which correlated to the IRIS study, the cumulative incidence of major molecular response was 70% and disappearance of BCR-ABL transcripts 30% to 50%.[7,27]

Nilotinib was approved for second-line treatment after Imatinib-resistance or -intolerance on the basis of the initial results of a phase 2 open-label study.[29,30]

In the 24-month follow-up analysis, CCyR was achieved in 51% of Imatinib-intolerant and 41% of Imatinib-resistant patients.[30,31]

In this study MMR achieved in 52% (11/21) patients who switch to Tasigna after Imatinib resistant or intolerance.

A significantproportion of patients with CML fail to take full advantage of TKI therapy only because of poor drug adherence duo to socioeconomic factors or factors related to the healthcare system, the patient, the drug, and the illness.[32]

Drug adherence in this study found in 68% (38/56) patients while treatment interruption and non-adherence to therapy was found in 32% (18/56) patients. Whereas in the ADAGIO study (The Adherence Assessment with Glivec: Indicators and Outcomes) only 14.2% of all patients were found to be close adherent to Imatinib, while 71% took less than the recommended dose and 14.8% took more.[33]

Poor adherence to Imatinib therapy has also been identified as the most important factor contributed to cytogenetic relapse and Imatinib failure.[5] In the ADAGIO study Patients with suboptimal response had significantly higher mean percentages of Imatinib not taken (23%).[33] In correlated with our result (21.4%) of patients on Imatinib failure to achieve target molecular response and need switch to second line duo to treatment interruption and non-adherence to therapy even with Health care coverage and freely provided expensive TKI.

In general non-adherence to TKI therapy in CML was correlated with poor therapeutic outcomes and increase of healthcare costs with these patients.[32] It is recognized that non-adherence to daily oral therapy can be a problem for long-term CML management even in populations with universal healthcare coverage.[34]

For that patient education on adherence to therapy, close monitoring of patients adherence and frequent molecular monitoring with Q PCR can help to identify non adherence to TKI therapy early in the treatment course.[5]

Therapy with TKIs is usually well tolerated, but adverse event may occur that leading to drug interruption and poor adherence. Imatinib is associated with mild-to-moderate side effects, including nausea, diarrhea, vomiting, muscle cramps, rashes, bone aches, leg or periorbital edema, and weight gain.[7,35] Mild to moderate peripheral edema occurred in the majority of patients also in our study peripheral edema was the most common adverse event associated with use of Imatinib.[9]

In most patients with Imatinib related side effect, switch to nilotinib lead to either resolved or improved of these adverse events. But new adverse event may be reported during Nilotinib therapy.[36]

To control the adverse effect associated with TKI, NCCN guideline provided specific recommendations for the management of side effect associated with TKI, By close

monitoring in grade 1/2 but in grade 3/4 required temporary drug discontinuation or dose reduction, and in some cases switch to an alternative TKI.[5,19]

## CONCLUSION

CML slightly male predominance, median age was 46 yearsyounger than that report in the United States and Europe. The majority of cases diagnosed in chronic phase. Response to TKI nearly similar to that report in international study. Most of patients who failed to achieve major molecular response to TKI were either poor drug adherence or intolerance. Therefore good drug adherence and sequential monitoring of patients with Q PCR can improve therapeutic effect of TKI therapy.

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